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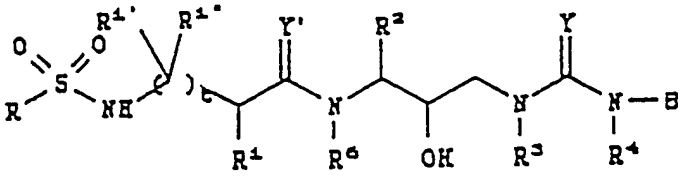
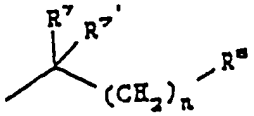


(I)



(II)

(57) Abstract

Compounds represented by formula (I) wherein B represents R^5 and radicals represented by formula (II) (values for the variables given herein), are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease.

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+ DESIGNATIONS OF "SU"

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RETROVIRAL PROTEASE INHIBITORS

This application is a continuation-in-part of U. S. Patent Application Serial No. 07/615,210, filed November 19, 1990.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to retroviral protease inhibitors and, more particularly, relates to novel compounds and a composition and method for inhibiting retroviral proteases. This invention, in particular, relates to urea-containing hydroxyethylamine protease inhibitor compounds, a composition and method for inhibiting retroviral proteases such as human immunodeficiency virus (HIV) protease and for treating a retroviral infection, e.g., an HIV infection. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

2. Related Art

During the replication cycle of retroviruses, gag and gag-pol gene products are translated as proteins. These proteins are subsequently processed by a virally encoded protease (or proteinase) to yield viral enzymes and structural proteins of the virus core. Most commonly, the gag precursor proteins are processed into the core proteins and the pol precursor proteins are processed into the viral enzymes, e.g., reverse transcriptase and retroviral protease. It has been shown that correct processing of the precursor proteins by the retroviral protease is necessary for assembly of infectious virons. For example, it has been shown that frameshift mutations in th protease region of the pol gene of HIV pr vents processing of the gag precursor prot in. Thus, attempts have been made to inhibit viral replication by inhibiting th action of retroviral proteases.

Retroviral protease inhibition typically involves a transition-state mimetic whereby the retroviral protease is exposed to a mimetic compound which binds (typically in a reversible manner) to the enzyme in competition with the gag and gag-pol proteins to thereby inhibit replication of structural proteins and, more importantly, the retroviral protease itself. In this manner, retroviral proteases can be effectively inhibited.

Several classes of mimetic compounds have been proposed, particularly for inhibition of proteases, such as for inhibition of HIV protease. Such mimetics include hydroxyethylamine isosteres and reduced amide isosteres. See, for example, EP O 346 847; EP O 342,541; Roberts et al, "Rational Design of Peptide-Based Proteinase Inhibitors, "Science, 248, 358 (1990); and Erickson et al, "Design Activity, and 2.8Å Crystal Structure of a C_2 Symmetric Inhibitor Complexed to HIV-1 Protease," Science, 249, 527 (1990).

Several classes of mimetic compounds are known to be useful as inhibitors of the proteolytic enzyme renin. See, for example, U.S. No. 4,599,198; U.K. 2,184,730; G.B. 2,209,752; EP O 264 795; G.B. 2,200,115 and U.S. SIR H725. Of these, G.B. 2,200,115, GB 2,209,752, EP O 264,795, U.S. SIR H725 and U.S. 4,599,198 disclose urea-containing hydroxyethylamine renin inhibitors. However, it is known that, although renin and HIV proteases are both classified as aspartyl proteases, compounds which are effective renin inhibitors generally cannot be predicted to be effective HIV protease inhibitors.

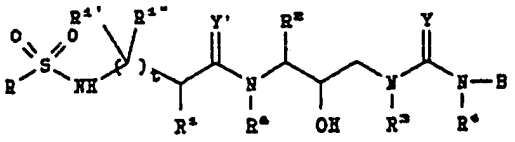
BRIEF DESCRIPTION OF THE INVENTION

The present invention is directed to virus inhibiting comp unds and compositions. More particularly, the pr sent invention is directed to retroviral protease inhibiting compounds and compositions, to a method f inhibiting retr viral proteases, to proc ss s for preparing th compounds and

to intermediates useful in such processes. The subject compounds are characterized as urea-containing hydroxyethylamine inhibitor compounds.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a retroviral protease inhibiting compound of the formula:



(Formula I)

or a pharmaceutically acceptable salt, prodrug or ester thereof wherein:

R represents alkyl, alkenyl, hydroxyalkyl, cycloalkyl, cycoalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaryl radicals;

t represents either 0 or 1;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, alkyl, alkenyl, alkynyl and cycloalkyl radicals and amino acid side chains selected from asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, leucine, isoleucine, allo-isoleucine, tert-leucine, phenylalanine, ornithine,alanine, histidine, norleucine, glutamine, valine, threonine, serine, aspartic acid, beta-cyano alanine and allo-threonine side chains;

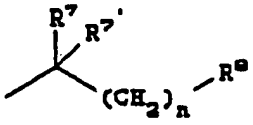
$R^{1'}$ and $R^{1''}$ independently represent hydrogen and radicals as defined f r R^1;

R^2 r presents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals ar ptionally substitut d with a group selected from $-OR^9$, $-SR^9$, and halogen radicals, wherein R^9 represents hydr gen and alkyl radicals;

R^3 represents alkyl, alkenyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, h terocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

Y and Y'independently represent O,S and NR^{15} wherein R^{15} represents radicals as defined for R^3;

B represents R5 and radicals represented by the formula:



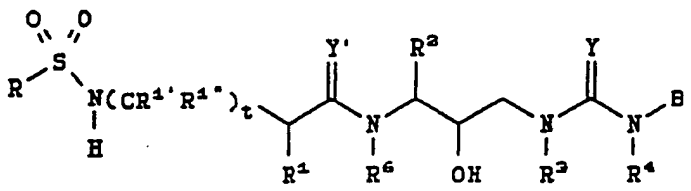
wherein

n represents an integer of from 0 to 6, R^7 and $R^{7'}$ independently represent radicals as defined for R^3 and amino acid side chains selected from the group consisting of valine, isoleucine, glycine, alanine, allo-isoleucine, asparagine, leucine, glutamine, and t-butylglycine or R^7 and $R^{7'}$ together with the carbon atom to which they are attached form a cycloalkyl radical; and R^8 represents cyano, hydroxyl, alkyl, alkoxy, cycloalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl radicals and radicals represented by the formulas $C(O)R^{16}$, CO_2R^{16}, SO_2R^{16}, SR^{16}, $CONR^{16}R^{17}$, OR^{16}, CF_3 and $NR^{16}R^{17}$ wherein R^{16} and R^{17} independently represent hydrogen and radicals as defined for R^3 or R^{16} and R^{17} together with a nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radicals.

R^4 and R^5 independently represent hydrogen and radicals as defined by R^3, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and heteroaryl radicals; and

R^6 represents hydrog n and radicals as defined for R^3.

A preferred class of retroviral inhibitor compounds of the present invention are those represented by the formula:



(Formula II)

or a pharmaceutically acceptable salt, prodrug or ester thereof, preferably wherein the stereochemistry about the hydroxy group is designated as (R);

R represents alkyl, alkenyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaryl radicals;

R^1 represents hydrogen, $-CH_2SO_2NH_2$, alkyl, alkenyl, alkynyl, and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, arnithine, histidine, norleucine glutamine, threonine, glycine, allo-threonine, serine, aspartic acid, beta-cyano alanine and valine side chains;

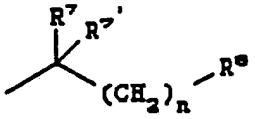
$R^{1'}$ and $R^{1''}$ independently represent hydrogen and radicals as defined for R^1;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl, and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl radicals, OR^9 and SR^9 wherein R^9 represents hydr gen and alkyl radicals, and halog n radicals;

R^3 represents alkyl, cycloalkyl, cycl alkylalkyl, h ter cycl alkyl, heterocycloalkylalkyl, aryl, heteroaryl, aralkyl and heter aralkyl radicals; and

R^4 represents hydrogen and radicals as defined for R^3;

B r presents radicals represented by th formula:



wherein n represents an integer of from 0 to 6, R^7 and $R^{7'}$ independently represent radicals as defined for R^3 and amino acid side chains selected from the group consisting of valine, isoleucine, glycine, alanine, allo-isoleucine, asparagine, leucine, glutamine, and t-butylglycine or R^7 and $R^{7'}$ together with the carbon atom to which they are attached form a cycloalkyl radical; and

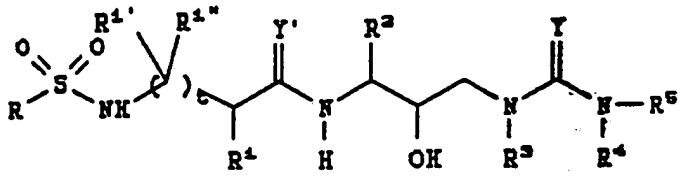
R^8 represents cyano, hydroxyl, alkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl radicals and radicals represented by the formulas $C(O)R^{16}$, CO_2R^{16}, SO_2R^{16}, SR^{16}, $CONR^{16}R^{17}$ and $NR^{16}R^{17}$, CF_3 wherein R^{16} and R^{17} independently represent hydrogen and radicals as defined for R^3 or R^{16} and R^{17} together with a nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radicals.

t represents 0 or 1;

Y and Y' independently represent O, S, and NR^{15} wherein R^{15} represents radicals as defined for R^3. Preferably, Y represents O.

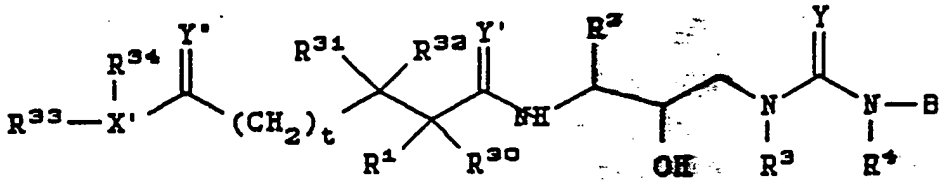
Preferably, R^3 represents radicals as defined above which contain no α-branching, e.g., as in an isopropyl radical or a t-butyl radical. The preferred radicals are those which contain a $-CH_2-$ moiety between the nitrogen of the urea and the remaining portion of the radical. Such preferred groups include, but are not limited t , benzyl, isoamyl, cyclohexylmethyl, 4-pyridylm thyl and the like.

Another preferred class of compounds are those r pr sented by th formula:



(Formula III)

or a pharmaceutically acceptable salt, prodrug or ester thereof wherein Y, Y', R, R^1, $R^{1'}$, $R^{1''}$, R^2, R^3, R^4, and R^5 are as defined above.



(Formula IV)

As utilized herein, the term "alkyl", alone or in combination, means a straight-chain or branched-chain alkyl radical containing from 1 to about 10, preferably from 1 to about 8, carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, octyl and the like. The term "alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like. The term "cycloalkyl" means an alkyl radical which contains from ab ut 3 t about 8

carbon atoms and is cyclic. The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical containing from about 3 to about 8, preferably from about 3 to about 6, carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, and the like. The term "aralkyl", alone or in combination, means an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, 2-phenylethyl and the like. The term "aralkoxy carbonyl", alone or in combination, means a radical of the formula -C(O)-O-aralkyl in which the term "aralkyl" has the significance given above. An example of an aralkoxycarbonyl radical is benzyloxycarbonyl. The term "aryloxy" means a radical of the formula aryl-o- in which the term aryl has the significance given above. The term "alkanoyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid, examples of which include acetyl, propionyl, butyryl, valeryl, 4-methylvaleryl, and the like. The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropanecarbonyl, cyclohexanecarbonyl, adamantanecarbonyl, and the like, or from a benz-fused monocyclic cycloalkanecarboxylic acid which is optionally substituted by, for example, alkanoylamino, such as 1,2,3,4-tetrahydro-2-naphthoyl,2-acetamido-1,2,3,4-tetrahydr -2-naphthoyl. The term "aralkan yl" m ans an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylac tyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-

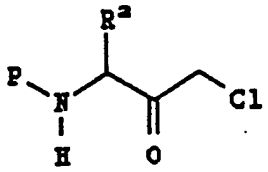
naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydroinnamoyl,4-methoxyhydrocinnamoyl, and the like. The term "aroyl" means an acyl radical derived from an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acids, an optionally substituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl, 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like. The heterocyclyl or heterocycloalkyl portion of a heterocyclylcarbonyl, heterocyclyloxycarbonyl, heterocyclylalkoxycarbonyl, or heterocyclyalkyl group or the like is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle which contains one or more hetero atoms selected from nitrogen, oxygen and sulphur, which is optionally substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo, and the like, and/or on a secondary nitrogen atom (i.e., -NH-) by alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom (i.e. = N-) by oxido and which is attached via a carbon atom. The heteroaryl portion of a heteroaroyl, heteroaryloxycarbonyl, or a heteroaralkoxy carbonyl group or the like is an aromatic monocyclic, bicyclic, or tricyclic heterocycle which contains the hetero atoms and is optionally substituted as defined above with respect to the definition of heterocyclyl. Examples of such heterocyclyl and heteroaryl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-yl, 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, furyl, thienyl, triaz lyl, xazolyl, thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolyl (.g., 2-quinolyl, 3-quinolyl, 1- xido-2-quinolyl, etc.), isoquin lyl (e.g., 1-isoquinolyl, 3-isoquinolyl, etc.), t trahydroquin lyl

(e.g., 1,2,3,4-tetrahydro-2-quinolyl, etc.), 1,2,3,4-tetrahydroisoquinolyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolyl, etc.), quinoxalinyl, β-carbolinyl, 2-benzofurancarbonyl, benzimidazolyl, and the like. The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkoxycarboxylic acid of the formula cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the significance given above. The term "aryloxyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the significance given above. The term "heterocyclyloxycarbonyl" means an acyl group derived from heterocyclyl-O-COOH wherein heterocyclyl is as defined above. The term "heterocyclylalkanoyl" is an acyl radical derived from a heterocyclyl-substituted alkane carboxylic acid wherein heterocyclyl has the significance given above. The term "heterocyclylalkoxycarbonyl" means an acyl radical derived from a heterocyclyl-substituted alkane-O-COOH wherein heterocyclyl has the significance given above. The term "heteroaryloxycarbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-O-COOH wherein heteroaryl has the significance given above. The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkanecarboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, and alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "halogen" means fluorine, chlorine, bromine or iodine. The term "leaving group" generally refers to groups readily displaceable by a nucleophile, such as an amine or an alcohol nucleophile. Such leaving groups are well kn wn and include carboxylates, N-hydroxysuccinimide, N-hydr xybenzotriazole, halides, triflates, tosylates -OR and -SR and the like. Preferred l aving gr ups are indicated herein where appropriate.

Proc dur s for preparing the compounds of Formula I are set forth below. It should be noted that the general procedure is shown as it relates to preparation of compounds having the specified stereochemistry, for example, wherein the stereochemistry about the hydroxyl group is designated as (R). However, such procedures are generally applicable, as illustrated in Example 45, to those compounds of opposite configuration, e.g., where the stereochemistry about the hydroxyl group is (S).

Preparation of Compounds of Formula I

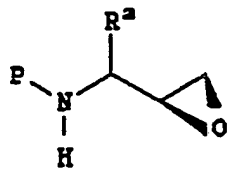
The compounds of the present invention represented by Formula I above can be prepared utilizing the following general procedure. An N-protected chloroketone derivative of an amino acid having the formula:



wherein P represents an amino protecting group, and R^2 is as defined above, is reduced to the corresponding alcohol utilizing an appropriate reducing agent. Suitable amino protecting groups are well known in the art and include carbobenzoxy, butyryl, t-butoxycarbonyl, acetyl, benzoyl and the like. A preferred amino protecting group is carbobenzoxy. A preferred N-protected chloroketone is N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone. A preferred reducing agent is sodium borohydrid . The r duction reaction is c nduct d at a temperature of fr m -10°C t ab ut 25°C, preferably at about 0°C, in a suitabl s lv nt system such as, for example, t trahydr furan, and th like. The N-pr tected chlor ket nes are commercially available from Bach m, Inc., T rrance, California. Alt rnatively,

the chloroketones can be prepared by the procedure set forth in S. J. Fittkau, J. Prakt. Chem., 315, 1037 (1973), and subsequently N-protected utilizing procedures which are well known in the art.

The resulting alcohol is then reacted, preferably at room temperature, with a suitable base in a suitable solvent system to produce an N-protected amino epoxide of the formula:



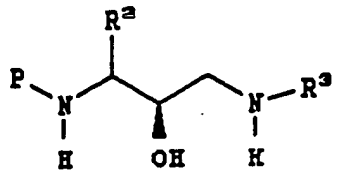
wherein P and R^2 are as defined above. Suitable solvent systems for preparing the amino epoxide include ethanol, methanol, isopropanol, tetrahydrofuran, dioxane, and the like including mixtures thereof. Suitable bases for producing the epoxide from the reduced chloroketone include potassium hydroxide, sodium hydroxide, potassium t-butoxide, DBU and the like. A preferred base is potassium hydroxide.

The amino epoxide is then reacted, in a suitable solvent system, with an excess of a desired amine of the formula:

$$R^3NH_2$$

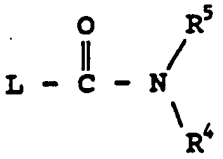
wherein R^3 is hydrogen or is as defined above. The reaction can be conducted over a wide range of temperatures, e.g., from about 10°C to about 100°C, but is preferably, but not necessarily, conducted at a temperature at which the solvent begins to reflux. Suitable solvent systems include th se wherein th solvent is an alc h l, such as m than l, ethanol, is pr pan l, and the like, ethers such as tetrahydrofuran, dioxane and the like, and toluene, N,N-dimethylf rmamide, dimethyl sulf xide, and mixtures

thereof. A pr ferred solvent is isopropanol. Exemplary amines corresponding to the formula R^3NH_2 include benzyl amine, isobutylamine, n-butyl amine, isopentyl amine, isoamylamine, cyclohexanemethyl amine, naphthylene methyl amine and the like. The resulting product is a 3-(N-protected amino)-3-(R^2)-1-(NHR^3)-propan-2-ol derivative (hereinafter referred to as an amino alcohol) is a novel intermediate and can be represented by the formula:



wherein P, R^2 and R^3 are as described above.

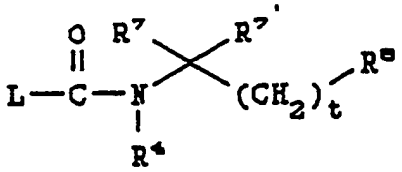
Where B represents R^5, the salt of the resulting amino alcohol can be reacted with an isocyanate of the formula R^4NCO where R^5 is hydrogen, or a compound of the formula



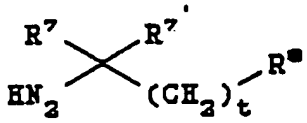
where R^5 is other than hydrogen. In this formula R^4 and R^5 are as described above and L represents a leaving group such as a halide, e.g., chloride, an imidazole radical, the radical p-NO_2-(C_6H_4)-O, and the like. A preferred group of this formula is a carbamoyl chloride. The corresponding sulfur analogs can also be utilized where Y is S. These reactions are conducted in suitable solvent systems such as methylene chloride and tetrahydrofuran.

A salt f the r sulting amin alc hol described above is th n reacted, in a suitable solvent system, with carb nyldiimidazole and an amin salt t

produce a urea derivative of the amino alcohol. This reaction can be represented as follows:

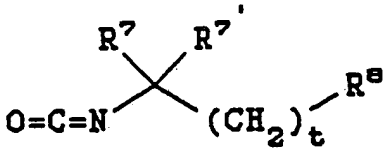


wherein R^4 is as described above and L represents a leaving group such as a halide, e.g., chloride, imidazole radical, the radical $p\text{-}NO_2\text{-}(C_6H_4)\text{-}O\text{-}$, and the like is prepared by reacting a carbonyldiimidazole with an amine salt, e.g., the hydrochloride salt of a compound represented by the formula:

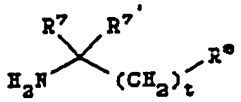


in a suitable solvent such as, for example, chloroform. The resulting product is then reacted with the salt, such as, for example, the hydrochloride salt, of the amino alcohol described above. The corresponding sulfur analogs can be utilized where Y of Formula II is S.

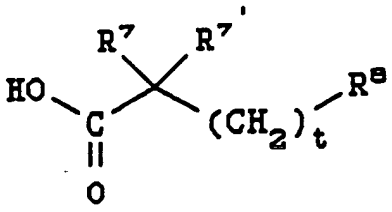
Alternatively, one can react the amino alcohol with an isocyanate of the formula:



either in the presence or absence of a suitable base, such as triethylamine, diisopropylethylamine, and the like in a suitable solvent such as toluene, methylene chloride, chloroform or tetrahydrofuran. The isocyanate can be readily prepared and isolated, if desired, by standard methods such as the reaction of an amine of the formula:



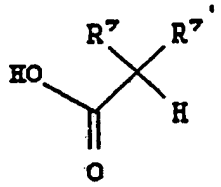
with phosgene or a phosgene equivalent, such as triphosgene, in the presence or absence of a suitable base, such as triethylamine, diisopropylamine and the like in a suitable solvent such as toluene, methylene chloride, chloroform or tetrahydrofuran. Alternatively, one can generate the isocyanate in situ by the Curtius rearrangement of a carboxylic acid of the formula:



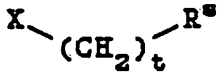
by an appropriate method. One such method is by the reaction of the carboxylic acid with diphenylphosphoryl azide in the presence of a suitable base, such as triethylamine or diisopropylethylamine, in a suitable solvent such as toluene, methylene chloride, chloroform and tetrahydrofuran and the like.

The carboxylic acids are either commercially available or can be prepared in a number of ways, which are known to those skilled in the art. For example, ne

can form the dianion of a carboxylic acid (or the monoanion of the corresponding ester) of the formula:

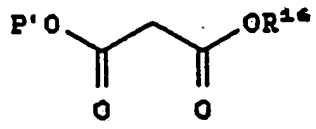


by deprotonation with a strong base, such as lithium diisopropyl amide or lithium hexamethyldisilazide, in a suitable solvent such as tetrahydrofuran and react the anion or dianion with an electrophilic reagent of the formula:



where X is an appropriate leaving group such as chloride, bromide, iodide, methanesulfonyl, p-toluenesulfonyl or trifluoromethanesulfonyl and the like.

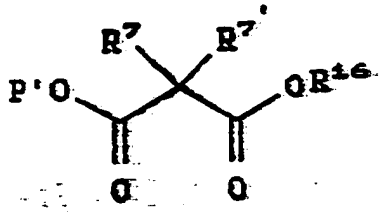
Alternatively, one can alkylate a diester of malonic acid of the formula:



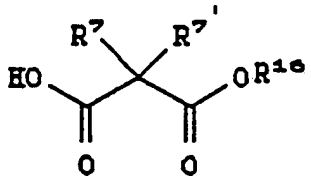
wher P' is a suitable acid pr tecting groups such as methyl, ethyl, isopropyl, benzyl, tertiary-butyl, trimethylsilyl, t-butyldimethylsilyl, and th like, with appropriate electr philes;

R^7-X $R^{7'}$-X

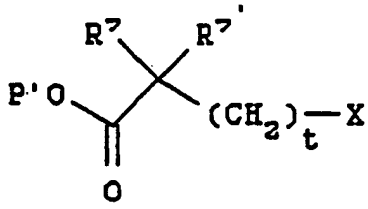
where R^7, $R^{7'}$ and X ar as defined above, in the presence of a suitable base such as sodium hydride, potassium hydride, sodium alkoxide or potassium alkoxide. Suitable alkoxides being methoxide, ethoxide, isopropoxide and tertiary-butoxide and the like. The reaction is carried out in a suitable solvent such as tetrahydrofuran, N,N-dimethylformamide or an alcohol solvent, such as methanol, ethanol, isopropanol or tertiary-butanol. The reaction with R^7 and $R^{7'}$ can be done sequentially if R^7 and $R^{7'}$ are different, or simultaneously if R^7 and $R^{7'}$ are identical or form a cyclic ring during the alkylation step. The resulting product is a mono- or di-substituted malonate diester of the formula:



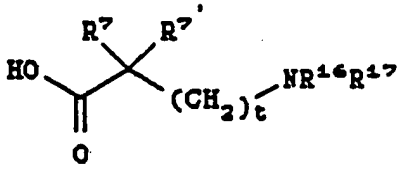
In order to generate the carboxylic acid required for the Curtius rearrangement, the acid protecting group P' is selectively removed. Suitable methods for removal are (1) hydrolysis with lithium hydroxide, sodium hydroxide, potassium hydroxide and the like, (2) acidolysis with an acid such as hydrochloric acid, hydrobromic acid, trifluoroacetic acid and the like, and (3) hydrogenolysis with hydrogen in the presence of a suitable catalyst such as palladium-on-carbon. The resulting carboxylic acid has the formula:



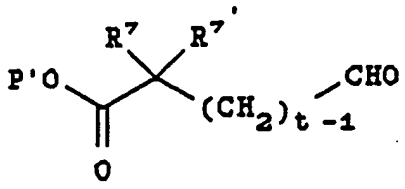
In the case where R^8 is an amino group $NR^{16}R^{17}$, the amino group an be introduced either by displacement of an appropriate leaving group or reductive amination with an appropriate aldehyde. The displacement of the leaving group from an ester of the formula:



where P' and X are as defined above, can be readily accomplished by one skilled in the art. The protecting group P' is then removed by the methods discussed above to provide the required carboxylic acid of the formula:

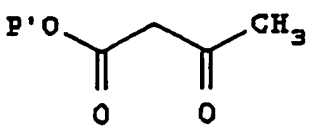


The reductive amination procedure is readily accomplished by the reaction of an aldehyde of the formula:

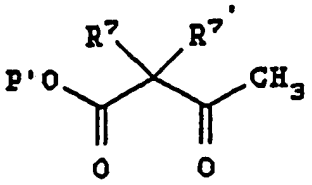


with the amine $HNR^{16}R^{17}$ in the presence of sodium cyanoborohydride or hydrogen and a suitable catalyst, such as palladium-on-carbon, and the acid protecting group P' is removed by the methods discussed above. The required aldehydes can be prepared by a number of methods well-known to those in the art. Such methods include reduction of an ester, oxidation of an alcohol or ozonolysis of an olefin.

In the case where R^8 is a keto-group and t is 0, one can mono- or dialkyate an ester of acetoacetic acid of the formula:

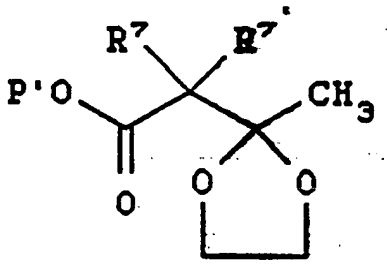


as described above for the malonate diesters to provide a compound of the formula:

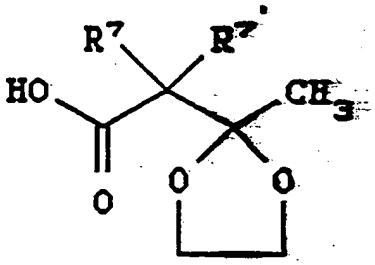


The acid protecting group can be removed to provide the desired carboxylic acid for the Curtius rearrangement, or the ketone can be converted to a ketal, such as the dimethyl ketal, diethyl ketal or ethylene glycol ketal,

by reaction with the appropriat alcohol in the presence of a suitable acid, such as p-toluenesulfonic acid or the like, and a dehydrating agent such as trimethyl- or triethylorthoformate to provide, for example, a compound of the following formula:

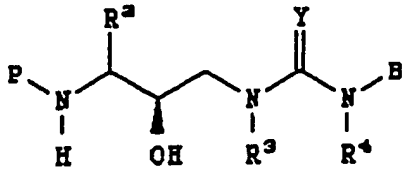


The protecting group P' can then be removed to provide a compound of the formula:

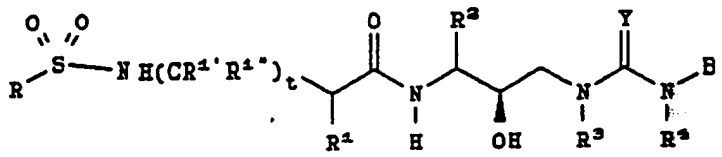


which is suitable for the Curtius rearrangement. If desired, the ketal group can be converted at any time during the subsequent synthesis to the corresponding ketone by hydrolysis in the presence of an acid such as aqueous hydrochloric acid.

The urea derivative of the amino alcohol, and the corresponding sulfur analog can be represented by the formula:



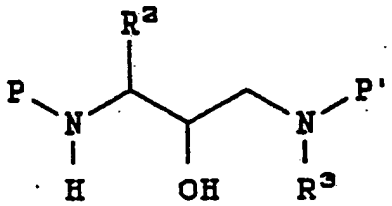
Following preparation of the urea derivative, or corresponding analogs wherein Y is S, the amino protecting group P is removed under conditions which will not affect the remaining portion of the molecule. These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of the protecting group, e.g., removal of a carbobenzoxy group, by hydrogenolysis utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. Where the protecting group is a t-butoxycarbonyl group, it can be removed utilizing an inorganic or organic acid, e.g., HCl or trifluoroacetic acid, in a suitable solvent system, e.g., dioxane or methylene chloride. The resulting product is the amine salt derivative. Following neutralization of the salt, the amine is then reacted with a substituted sulfonyl derivative of an amino acid or corresponding analog or derivative thereof represented by the formula ($RSO_2N[CR^{1'}R^{1''}]_tCH(R^1)COOH$) wherein t, R^1, $R^{1'}$ and $R^{1''}$ are as defined above, to produce the antiviral compounds of the present invention having the formula:



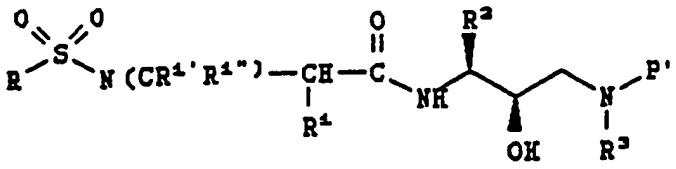
wherein t, B, R, R^1, $R^{1'}$, $R^{1''}$, R^2, R^3, R^4, and Y are as defined above. The sulfonyl derivative of the amin

acid or corresponding analog or derivative thereof is reacted with a substituted sulfonyl chloride (RSO_2CL) at a suitable pH value, e.g. pH9, to produce the corresponding sulfonamide. Alternatively, the amine salt can be reacted with a protected amino acid and the resulting compound deprotected and then reacted with a sulfonyl chloride. Where the amine is reacted with a substituted sulfonyl derivative of an amino acid, e.g., when t=1 and $R^{1'}$ and $R^{1''}$ are both H, so that the amino acid is a β-amino acid, such β-amino acids can be prepared according to the procedure set forth in a copending application, U. S. Serial No. 07/345,808. Where t is 1, one of $R^{1'}$ and $R^{1''}$ is H and R^1 is hydrogen so that the amino acid is a homo-β-amino acid, such homo-β-amino acids can be prepared by the same procedure. Where t is 0 and R^1 is alkyl, cycloalkyl, $-CH_2SO_2NH_2$ or an amino acid side chain, such materials are well known and many are commercially available from Sigma-Aldrich.

Alternatively, the protected amino alcohol from the epoxide opening can be further protected at the newly introduced amino group with a protecting group P' which is not removed when the first protecting P is removed. One skilled in the art can choose appropriate combinations of P and P'. One suitable choice is when P is Cbz and P' is Boc. The resulting compound represented by the formula:



can be carried through the remainder of the synthesis to provide a compound of the formula:



and the new protecting group P' is selectively removed, and following deprotection, the resulting amine reacted to form the urea derivative as described above. This selective deprotection and conversion to the urea can be accomplished at either the end of the synthesis or at any appropriate intermediate step if desired. This alternate procedure is also suitable for producing compounds of formula III.

It is contemplated that for preparing compounds of the Formulas having R^6, the compounds can be prepared following the procedure set forth above and, prior to coupling the urea derivative or analog thereof to the amino acid $PNH(CH_2)_tCH(R^1)COOH$, carried through a procedure referred to in the art as reductive amination. Thus, a sodium cyanoborohydride and an appropriate aldehyde $R^6C(O)H$ or ketone $R^6C(O)R^6$ can be reacted with the urea derivative compound or appropriate analog at room temperature in order to reductively aminate any of the compounds of Formulas I-VI. It is also contemplated that where R^3 of the amino alcohol intermediate is hydrogen, the inhibitor compounds can be prepared through reductive amination of the final product of the reaction between the amino alcohol and the amine or at any other stage of the synthesis for preparing the inhibitor comp unds.

Contemplated equivalents of the g neral formulas set forth ab v f r the antiviral compounds and derivatives as well as the interm diates are compounds th rwise corresponding theret and having the same

general properties wherein one or mor of the various R groups are simple variations of the substituents as defined therein, e.g., wherein R is a higher alkyl group than that indicated. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, amino and the like functional group, is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

The chemical reactions described above are generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting materials are known or readily preparable from known starting materials.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and n t limitative f the remainder of th disclosure in any way whatsoever.

All reagents were used as received without purificati n. All prot n and carbon NMR spectra w r

obtained on either a Varian VXR-300 or VXR-400 nuclear magnetic resonance spectrometer.

Example 1

This example illustrates preparation of compounds of the present invention.

a) The procedure described below was used to prepare (2R,3S)-3-[N-(n-butylsulfonyl)-L-tert-butylglycyl]amido-1-isoamyl-1-(tert-butylcarbamyl)amino-4-phenyl-2-butanol.

A solution of N-(n-butylsulfonyl)-L-tert-butylglycine (431.6 mg, 1.79 mmol), N-hydroxybenzotriazole (HOBT) (351.0 mg, 2.29 mmol), and 1-(3-dimethylaminopropyl)-3-ethylarbodiimide hydrochloride (EDC) (361.9 mg, 1.86 mmol) in 3 mL of anhydrous dimethylformamide (DMF) cooled to 0°C and stirred under nitrogen for 0.5 h. This solution was then treated with (2R,3R)-3-amino-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol (601.4 mg, 1.75 mmol) prepared as in Example 9, and stirred at room temperature for 16 h. The solution was poured into 50 mL of 60% saturated aqueous sodium bicarbonate solution. The aqueous solution was then extracted three times with dichloromethane, the combined organic extract was washed with 10% aqueous citric acid, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give 670.0, 66% of (2R,3S)-3-[N-(n-butylsulfonyl)-L-tert-butylglycyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol, mass spectrum (MH+) calc'd. for $C_{30}H_{55}N_4O_5S$: 583.3893. Found: 583.3893.

b) The procedure described below was used to prepare (2R,3S)-3-[N-(E)-2-phenylethenesulfonyl-L-valyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol.

A solution of N-(E)-2-phenylethenesulfonyl-L-valine (386.9 mg, 1.54 mmol) N-hydroxybenzotriazole (HOBT) (317.8 mg, 2.08 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (325 mg, 1.67 mmol) in 3 mL of anhydrous

dimethylformamide (DMF) cooled to 0°C and stirred under nitrogen for 0.5 h. This solution was then treated with (2R,3R)-3-amino-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol (530.5 mg, 1.54 mmol), prepared as in Example 2, and stirred at room temperature for 16 h. The solution was poured into 50 mL of 60% saturated aqueous sodium bicarbonate solution. The aqueous solution was then decanted from the organic residue. the organic residue was taken up in dichloromethane and washed with 10% aqueous citric acid, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give 690 mg, 71% of (2R,3S)-3-[N-(E)-2-phenylethenesulfonyl-L-valyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol, mass spectrum (MH+) calc'd. for $C_{33}H_{50}N_4O_5S$: 615.3580. Found: 615.3580.

c) The procedure described below was used to prepare (2R,3S)-3-[N-(E)-2-phenylethenesulfonyl-L-tert-butylglycyl]amido-1-isoamyl-1-(tert-butylarbamoyl)amino-4-phenyl-2-butanol.

A solution of N-(E)-2-phenylethenesulfonyl-L-tert-butylglycine (102. mg, 0.35 mmol), N-hydroxybenzotriazole (HOBT) (73.5 mg, 0.49 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (69.8 mg. 0.36 mmol) in 2 mL of anhydrous dimethylformamide (DMF) cooled to 0°C and stirred under nitrogen for 0.5 h. This solution was then treated with (2R,3R)-3-amino-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol (120.8 mg, 0.35 mmol), prepared as in Example 2, and stirred at room temperature for 16 h. The solution was poured into 50 mL of 60% saturated aqueous sodium bicarbonate solution. The aqueous solution was then decanted from the organic residue. The organic residue was taken up in cichlor methane and washed with 10% aqueous citric acid, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give 100 mg, 45% f (2R,3S)-3-[N-(E)-2-phenylethenesulfonyl)-L-tert-butylglycyl]amido-1-is amyl-1-(tert-butylcarbamoyl)amin -4-phenyl-2-butanol,

mass spectrum (MH+) calc'd. for $C_{34}H_{52}N_4O_5S$: 629.3734. Found: 629.3734.

d) The procedure described below was used to prepare (2R,3S)-3-[N-(E)-2-phenylethenesulfonyl-L-alanyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol.

A solution of N-(E)-2-phenylethenesulfonyl-L-alanine (165. mg, 0.65 mmol), N-hydroxybenzotriazole (HOBT) (160.8 mg, 1.06 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (137.3 mg,0.70 mmol) in 7 mL of anhydrous dimethylformamide (DMF) cooled to 0°C and stirred under nitrogen for 0.5 h. This solution was then treated with (2R,3R)-3-amino-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol (224.4 mg, 0.65 mmol), prepared as in Example 2, and stirred at room temperature for 16 h. The solution was poured into 50 mL of 60% saturated aqueous sodium bicarbonate solution. the aqueous solution was then decanted from the organic residue. The organic residue was taken up in dichloromethane and washed with 10% aqueous citric acid, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give 110 mg, 29% of (2R,3S)-3-[N-(E)-2-phenylethenesulfonyl)-L-alanyl]amido-1-isoamyl-1-(tert-butylcarbomoyl) amino-4-phenyl-2-butanol, mass spectrum (MLi+) calc'd. for $C_{31}H_{46}N_4O_5SLi$: 593.3349. Found: 593.3315.

e) The procedure described below was used to prepare (2R,3S)-3-[N-2-napthylsulfonyl-L-valyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol.

A solution of N-(E)-2-napthylsulfonyl-L-valine (374.5 mg, 1.22 mmol) N-hydroxybenzotriazole (HOBT) (164.8 mg, 1.09 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (233.5 mg, 1.20 mmol) in 2 mL of anhydrous dimethylformamide (DMF) cooled to 0°C and stirred under nitrogen for 0.5 h. This solution was then treated with (2R,3R)-3-amino-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol

(415.8 mg, 1.21 mmol), prepared as in Example 2, and stirred at room temperature for 16 h. The solution was poured into 50 mL of 60% saturated aqueous sodium bicarbonate solution. The aqueous solution was then decanted from the organic residue. The organic residue was taken up in dichloromethane and washed with 10% aqueous citric acid, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give 660 mg, 85% of (2R,3S)-3-[N-2-napthylsulfonyl-L-valyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol, mass spectrum (MH+) calc'd. for $C_{35}H_{50}N_4O_5S$: 639.3580. Found: 639.3580.

f) The procedure described below was used to prepare (2R,3S)-3-[N-2-napthylsulfonyl-L-alanyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol.

A solution of N-(E)-2-napthylsulfonyl-L-alanine (638.1 mg, 2.28 mmol) N-hydroxybenzotriazole (HOBT) (466.1 mg, 3.09 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (484.1 mg, 2.49 mmol) in 12 mL of anhydrous dimethylformamide (DMF) cooled to 0°C and stirred under nitrogen for 0.5 h. This solution was then treated with (2R,3R)-3-amino-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol (786.0 mg, 2.28 mmol), prepared as in Example 2, and stirred at room temperature for 16 h. The solution was poured into 50 mL of 60% saturated aqueous sodium bicarbonate solution. The aqueous solution was then decanted from the organic residue. The organic residue was taken up in dichloromethane and washed with 10% aqueous citric acid, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give a white solid which was isolated by filtration and air dried to give 410 mg, 30% of (2R,3S)-3-[N-2-napthylsulfonyl-L-alanyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol, mass spectrum (MH+) calc'd. for $C_{33}H_{46}N_4O_5S$: 611.3267. Found: 611.3267.

g) The procedure described bel w was used to prepare (2R,3S)-3-[N-2-napthylsulf nyl-L-tert-butylglycyl]amido-

1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol.

A solution of N-(E)-2-napthylsulfonyl-L-tert-butylglycine (49.1 mg, 0.15 mmol) N-hydroxybenzotriazole (HOBT) (31.5 mg, 0.21 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (32.1 mg, 0.16 mmol) in 1 mL of anhydrous dimethylformamide (DMF) cooled to 0°C and stirred under nitrogen for 0.5 h. This solution was then treated with (2R,3R)-3-amino-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol (53.6 mg, 0.15 mmol), prepared as in Example 2, and stirred at room temperature for 16 h. The solution was poured into 5.0 mL of 60% saturated aqueous sodium bicarbonate solution. The aqueous solution was then decanted from the organic residue. The organic residue was taken up in dichloromethane and washed with 10% aqueous citric acid, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give a white solid which was isolated by filtration and air dried to give 74.1 mg, 30% of (2R,3S)-3-[N-2-napthylsulfonyl-L-tert-butylglycyl]amido-1-isoamyl-1-(tert-butylarbamoyl)amino-4-phenyl-2-butanol, mass spectrum (MH+) calc'd. for $C_{32}H_{53}N_4O_5S$: 653.3736. Found: 653.3736.

h) The procedure described below was used to prepare (2R,3S)-3-(N-methanesulfonyl-L-asparaginyl)amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol.

A solution of (2R,3S)-3-(N-L-asparaginyl)amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol (260 mg, 0.56 mmol), prepared as in Example 2, and triethylamine (2 equivalents) in 1 mL of tetrahydrofuran (THF) was treated with methanesulfonyl chloride (70 mg, 0.61 mmol). The solution was maintained at room temperture for 16 h and then concentrated *in vacuo*. The residue was taken up in dichloromethane, washed with saturated aqueous sodium bicarbonate, 1 N aqueous potassium bisulfate, saturated aqueous sodium chloride, dried over

anhydrous magnesium sulfate, filtered and concentrated to give 180 mg, 59% of (2R,3S)-3-(N-methanesulfonyl-L-asparaginyl)amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol, FAB mass spectrum (MH+) = 542.

i) The procedure described below was used to prepare (2R,3S)-3-(N-methanesulfonyl-L-tert-butylglycyl)amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol.

A solutio of N-methanesulfonyl-L-tert-butylglycine (237.7 mg, 1.14 mmol), N-hydroxybenzotriazole (HOBT) (262.4 mg, 1.74 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (243.3 mg, 1.25 mmol) in 6 mL of anhydrous dimethylformamide (DMF) cooled to 0°C and stirred under nitrogen for 0.5 h. This solution was then treated with (2R,3R)-3-amino-1-iwoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol (390.8 mg, 1.13 mmol), prepared as in Example 2, and stirred at room temperatre for 16 h. The solution was poured into 30 mL of 60% saturated aqueous sodium bicarbonate solution. The aqueous solution was then decanted from the organic residue. The organic residue was taken up in dichloromethane and washed with 10%aqueous citric acid, brine, dried anhydrous magnesium sulfate, filtered and concentrated to give 435.8 mg, 72% of (2R,3S)-3-(N-methanesulfonyl-L-tert-butylglycyl)amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol, mass spectrum (MH+) calc'd. for $C_{27}H_{48}N_4O_5S$: 541.3424. Found: 541.3424.

j) The procedure described below was used to prepare (2R,3s)-3-(N-2-phenylethanesulfonyl-L-alanyl)amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol.

A solution of (2R,3S)-3-[N-(E)-2-phenylethenesulfonyl)-L-alanyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butan 1 (250 mg, 0.43 mm 1), prepared as in Example 2, in 20 mL f methanol was charged into a Fisher-Porter bottle along with 10%

palladium on carbon atalyst under a nitrogen atmosphere. The reaction vessel was sealed and flushed five times with nitrogen and then five times with hydrogen. The pressure was maintained at 50 psig for 16 h and then the hydrogen was replaced with nitrogen and the solution filtered through a pad of celite to remove the catalyst and the filterate concentrated *in vacuo* to give 200 mg, 79% of (2R,3S)-3-(N-2-phenylethanesulfonyl-L-alanyl)amido-1-isoamyl-1-(tert-butylarbamoyl)amino-4-penyl-2-butanol, FAB mass spectrum (MLi+) = 595.

k) The procedure described below was used to prepare (2R,3S)-3-(N-2-phenylethanesulfonyl-L-valyl)amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol.

A solution of (2R,3S)-3-[N-(E)-2-phenylethenesulfonyl-L-valyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol. (300 mg, 0.49 mmol) in 20 mL of methanol was chrged into a Fisher-Porter bottle along with 10% palladium on carbon catalyst under a nitrogen atmosphere. The reaction vessel was sealed and flushed five times with nitrogen and then five times with hydrogen. The pressure was maintained at 50 psig for 16 h and then the hydrogen was replaced with nitrogen and the solution filtred through a pad of celite to remove the catalyst and the filterate concentrated *in vacuo* to give 280 mg, 93% of (2R,3S)-3-(N-2-phenylethanesulfonyl-L-valyl)amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol, FAB mass spectrum (ML+) = 623.

l) The procedure described below was used to prepare (2R,3S)-3-(N-2-phenylethanesulfonyl-L-tert-butylglyhcyl)amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol.

A solution f (2R,3S)-3-[N-(E)-2-phenyl thenesulfonyl-L-tert-butylglycyl]amido-1-isoamyl-1-(trt-butylcarbam yl)amino-4-phenyl-2-butanol. (150 mg, 0.24 mm l) in 20 mL of methanol was charged into a Fisher-Porter b ttle along with 10% palladium on carbon catalyst under a nitrogen atmosphere. The reaction

vessel was sealed and flushed five times with nitrogen and then five times with hydrogen. The pressure was maintained at 50 psig for 16 h and then the hydrogen was replaced with nitrogen and the solution filtred through a pad of celite to remove the catalyst and the filterate concentrated *in vacuo* to give 140 mg, 92% of (2R,3S)-3-(N-2-phenylethanesulfonyl-L-tert-butylglycyl)amido-1-isoamyl-2-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol, FAB mass spectrum (MLi+) = 637.

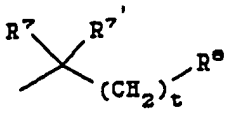
m) The procedure described below was used to prepare (2R,3S)-3-(N-2-phenylethanesulfonyl-L-asparaginyl)amido-2-isoamyl-2-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol).

A solution of (2R,3S)-3-[N-(E)-2-phenylethenesulfonyl-L-asparaginyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol. (50 mg, 0.79 μmol) in 20 mL of methanol was chrged into a Fisher-porter bottle along with 10% palladium on carbon catalyst under a nitrogen atmosphere. The reaction vessel was sealed and flushed five times with nitrogen and then five times with hydrogen. The pressure was maintained at 50 psig for 16 h and then the hydrogen was replaced with nitrogen and the solution filtered through a pad of celite to remove the catalyst and the filterate concentrated *in vacuo* to give 40 mg, 80% of (2R,3S)-3-(N-2-phenylethanesulfonyl-L-asparaginyl)amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol, FAB mass spectrum (MH+)=632.

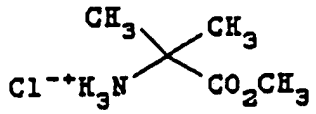
Following the procedure shown above, many of the compounds shown in the remaining examples could be prepared as sulfonamides.

Example 2A

This example illustrates preparation of compounds wherein B represents:

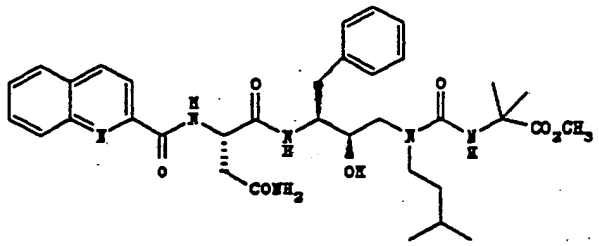


Methyl aminoisobutyrate hydrochloride.



A 500 mL round bottomed flask equipped with nitrogen inlet, thermometer adapter, solids addition funnel, and magnetic stirrer was placed in an ice salt bath and charged with 100 mL of methanol. To this solution was added thionyl chloride(18.0 mL, 0.25 mol) via syringe at such a rate that the internal temperature was maintained at less than 0 °C. This solution was then treated with aminoisobutyric acid(19.6g, 0.19 mol) portion wise from the addition funnel at such a rate that the temperature did not rise above 5 °C. The ice bath was removed and replaced with an oil bath and the solution warmed to 50 °C for 1h and then concentrated *in vacuo*. The salt was thoroughly dried under vacuum to give the desired product as a white solid 28g, 96%, mp 185 °C. ^{1}H nmr ($CDCl_3$) 300 MHz 8.87(brs, 3H), 3.74(s, 3H), 1.65(s, 6H).

2,5,9,11-Tetraazatridecan-13-oic acid, 3-(2-amino-2-oxoethyl)-7-hydroxy-12,12-dimethyl-9-(3-methylbutyl)-1,4,10-trioxo-6-(phenylmethyl)-1-(2-quinolinyl)-methyl ester, [3S-(3R*,6R*,7S*)]-



A 100 mL round bottomed flask equipped with a reflux condenser, nitrogen inlet, and magnetic stir bar was charged with methyl aminoisobutyrate hydrochloride (298 mg, 1.95 mmol) and 30 mL of chloroform. The slurry was warmed to reflux whereupon the salt dissolved and then the solution was treated with carbonyldiimidazole (317 mg, 1.95 mmol) and maintained at this temperature for 40 m. In a separate 50 mL round bottomed flask was placed the hydrochloride of (2R,3S)-3-amino-1-(3-methylbutyl)-1-[(1,1-dimethylethyl)amino] carbonyl)-4-phenyl-2-butanol (910 mg, 1.68 mmol), 20 mL of chloroform and triethylamine (648 mg, 6.40 mmol). This mixture was stirred at room temperature for 30 m and then added to the 100 mL round bottomed flask. The entire mixture was heated to 50 °C for 16 h and then poured into a separatory funnel. The mixture was diluted with 5% aq. citric acid and the phases separated. The organic phase was washed with an additional portion of citric acid, sat. aq. $NaHCO_3$, brine, dried over anhyd. $MgSO_4$, filtered and concentrated *in vacuo* to give a white solid, 820 mg, 75%, that was further purified by flash chromatography over SiO_2 eluting with methanol/CH_2Cl_2. The pure product was is lated by concentration f the appropriate fracti n, 410 mg, 38% yield along with 150 mg of 95% pure product.

Example 2B

General Procedure for Curtius Rearrangement and Reaction with Amino Alcohol Derivative.

To a solution of 1 mmol of carboxylic acid in 12 mL of toluene and 3 mmol of triethylamine at 90°C under a nitrogen atmosphere, was added 1 mmol of diphenylphosphoryl azide. After 1 hour, a solution of 1 mmol of amino alcohol derivativbe in 3.5 mL of either N,N-dimethylformamide or toluene was added. After 1 hour, the solvent was removed under reduced pressure, ethyl acetate and water added and the layers separated. The organic layer was washed with 5% citric acid, sat d sodium bicarbonate, brine, dried, filtered and concentrated to afford the crude product. This was then recrystallized or chromatographed on silica gel to afford the purified final compound.

Preparation of mono-tertiary-butyl 2,2-dimethylmalonate.

To a solution of mono-methyl mono-t-butyl malonate (20.5g, 117.7 mmol) in THF (275 ml) was added NaH (2.95g, 117.7 mmol) in portions at 0°C over 15 min then stirred at r.t. for 30 min. The mixture was then cooled to 0°C and to this was added MeI (7.5 ml, 118 mmol) slowly and stirred at r.t. for 1 h. After it was cooled to 0°C, to this cold solution was added NaH (2.95g, 118 mmol) then MeI (7.5 ml, 118 mmol) by following the procedure described above. A usual workup (10 ml sat. NH_4Cl, 100 ml Et_2O-pet ether, 5% HCl, 5% $NaHCO_3$, finally sat. NaCl) gave 16.2g (68%) of desired product as a pale yellow oil. The oil (10.1g, 50.0 mmol) was dissolved in MeOH (150 ml) and to this was added 1.25N NaOH (20 ml of 2.5N NaOH with 20 ml of H_2O, 50.0 mmol) over a period of 2 h and stirred at 0°C for 3 h and r.t. for 16 h. Removal of solvents in vacuo (<40°C) gave an oil. The oil was dissolved in water (125 ml) and extracted with Et_2O (25 ml). Th aqueous layer was collected and acidified with 6N HCl (a white precipitate was f rm d imm diately) t pH ~ 1 and extracted with Et_2O (75 ml x

3). The combined extracts were washed with sat. NaCl (50 ml), dried (Na_2SO_4) and concentrated to afford 7.1g (75%) of mono-tertiary-butyl 2,2-dimethylmalonate as a white solid.

Preparation of 2,2-Dimethylmalonate, mono-ethyl ester.

To a suspension of NaH (2.5g, 95%, 100 mmol) in dry THF (200 ml) was added diethylmalonate (8.0g, 50 mmol) slowly at 0°C and stirred at r.t. for 1 h. The solution was cooled to 0°C and to this was added a solution of MeI (14.9g, 105 mmol) in THF (20 ml) slowly. The mixture was stirred at 0°C for 1 h, r.t. for 2 h and diluted with Et_2O-Pet ether (5:1, 150 ml) then washed with H_2O (80 ml) and sat. NaCl solution (50 ml). The organic phase was separated, dried (Na_2SO_4) and concentrated to afford 8.2g (87%) of desired product as an oil. This oil was dissolved in EtOH (50 ml) and cooled to 0°C. To this cold solution was added 10% NaOH (20 ml, 50 mmol) dropwise at 0°C and stirred at 0°C for 2 h, at r.t. for 16 h. Removal of solvents gave an oil. The oil was dissolved in H_2O (40 ml) and Et_2O (20 ml). The aqueous layer was separated and acidified with 6N HCl to pH ~ 1 then extracted with ether (50 ml x 2). The combined extracts were washed with sat. NaCl (20 ml), dried (Na_2SO_4) and concentrated to afford 6.5g (81%) of desired acid as an oil.

Preparation of 2-Ethyl-2-methylmalonate, mono-ethyl ester.

To a suspension of NaH (1.25g, 95%, 50 mmol) in dry THF (200 ml) was added diethylmalonate (8.0g, 50 mmol) slowly at 0°C. The reaction mixture was allowed to warm up to r.t. and stirred for 1 h then cooled to 0°C. To this cold solution was added MeI (7.1g, 50 mmol) dropwise. After the resulting mixture was stirr d at r.t. f r 2 h, it was cooled to 0°C. To the c ld s lution was added EtBr (5.6g, 5.1 mmol) and stirred at

r.t. for 2 h. The mixture was diluted with ether-Pet ether (5:1, 150 ml) and washed with H_2O (50 ml), sat. NaCl solution, dried (Na_2SO_4) and concentrated to afford 10g (99%) of desired product as an oil. This oil was dissolved in EtOH (50 ml) and cooled to 0°C. To this cold solution was added 10% NaOH (20 ml, 50 mmol) dropwise via an additional funnel and stirred at 0°C for 2 h, at r.t. for 16 h. Removal of solvents gave an oil. The oil was dissolved in H_2O (40 ml) and Et_2O (20 ml). The aqueous layer was separated and acidified with 6N HCl to pH ~ 1 then extracted with ether (50 ml x 2). The combined ether solutions were washed with sat. NaCl (20 ml), dried (Na_2SO_4), and concentrated to afford 7.2g (83%) of desired acid as an oil.

<u>Preparation of 2,2-Dimethyl-3-(4-morpholinyl)propionic Acid.</u>

Dissolve 2.62 ml (30 mmoles,1.2eq.) oxalyl chloride in anhydrous CH_2Cl_2. Cool to -78 degrees C under N_2. Slowly add 2.66 ml (37.5 mmoles,1.5eq.) DMSO. Stir 15 minutes. To this solution add 3.19 ml (25 mmoles,1.0 eq.) methyl 2,2 dimethyl-3-hydroxypropionate. Stir an additional hour at -78 degrees. Quench reaction with 13.94 ml (100 mmoles,4.0 eq.) triethylamine. Warm to room temperature. Wash organic layer 1x0.1NHCl, 1x saturated sodium bicarbonate, 1x saturated NaCl. Dry with $MgSO_4$ and rotovap. Yield=69% M+H=131

Dissolve 1.00ml (11.53 mmoles, 3eq.) morpholine in 43ml 1% AcOH/MeOH. Add 500mg (3.83 mmoles, 1eq.) aldehyde from above. Cool to 0 degrees C under N_2. Slowly add 362.0mg (5.76 mmoles,1.5eq) $NaCNBH_3$. Stir 2-3 days. Strip off MeOH. Diss lve in minimum H_2O. Add Conc HCl to pH=2. Wash 2xEt_2O. Add 6N NaOH to aqu ous layer t pH>9. Extract 3xEtOAc. Dry with $MgSO_4$ and rotovap. Purify by silica flash chr matography (60:1 $CH2Cl_2$:CH_3OH) Yield=18% M+H=202

Dissolve 337mg (1.7mmoles, 1eq) methyl ester from above in 18ml AcOH. Add 4.5ml HCl. Heat to 60 degrees C. under N_2. Stir overnight. Rotovap off solvent. Azeotrope with toluene. Rotovap 1x 4N HCl/ dioxane. Desscicate over P_2O_5 overnight. Yield=94% M+H=188

Preparation of 2,2-dimethyl-4-(1-methylpiperazinyl)butanoic acid.

A mixture of 2,2-dimethylpentenoic acid (5.66g, 42 mmol) BnBr (6.84g, 40 mmol) K_2CO_3 (5.8g, 42 mmol) and NaI (3g, 20 mmol) in acetone (65 ml) was heated to reflux (oil bath 80°C) for 16 h. The acetone was stripped off and the residue was dissolved in H_2O (20 ml) and ether (60 ml). The ether layer was separated, dried (Na_2SO_4) and concentrated to afford 8.8g (100%) of desired ester as an oil.

To a solution of ester from above (8.8g, 40.0 mmol) in CH_2Cl_2 (150 ml) was bulbed through a stream of ozone at -78°C until the blue color persisted. Excess ozone was removed by a stream of N_2, dimethylsulfide (10 ml) was added, and the reaction mixture was allowed to warm to room temperature and stirred for 56 h. After the removal of solvents, the residue was dissolved in Et_2O (50 ml) and washed with H_2O (15 ml) then sat. NaCl soltuion (10 ml). The organic layer was dried (Na_2SO_4) concentrated to afford 8.2 g (93%) of aldehyde as an oil.

To a solution of aldehyde from above (4.2g, 19.1 mmol) in MeOH (80 ml) was added $NaCNBH_3$ (2.4g, 38.2 mmol) and acetic acid (2 ml) at 0°C. To this cold solution was added N-methylpiperizine (2.5g, 25 mmol) slowly at 0°C. The reaction mixture was stirred at 0°C for 2 h and room temperature for 16 h. The removal of solvents gave a solid. To the s lid was added H_2O (25 ml) and eth r (50 ml). The organic layer was s parated and to this was added 5% HCl (25 ml). The aqueous layer was c llected

and to this was added 2.5N NaOH until pH ~ 14, and extracted with ether (25 ml x 3). The combined organic extracts were washed with brine (15 ml), dried (Na_2SO_4) and concentrated to afford 5.5g (95%) of desired amine as an oil. This oil was hydrogenated (1.5g of 10% Pd/C, 50 psi H_2) in MeOH (50 ml) at room temperature for 2 h. the reaction mixture was filtered and the filtrate was concentrated to afford 4.0g (98%) of the desired amino acid as a white solid.

Preparation of 2,2-dimethyl-6-(4-morpholinyl)-4-oxohexanoic acid.

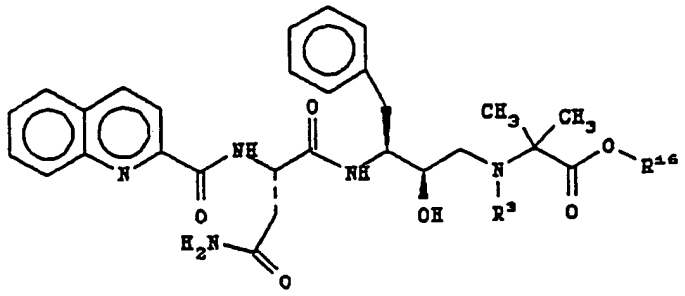
To a suspension of NaH (1.5g, 60.0 mmol) in THF (155 ml) was added a solution of methyl 2,2-dimethyl-3-hydroxypropionate (6.6g, 50.0 mmol) slowly at 0°C. After the addition was completed, the reaction mixture was stirred at room temperature fo 1 1/2 h. It was cooled to 0°C. To this cold solution was added allyl bromide (7.3g, 60.0 mmol) slowly and NaI (150 mg) in one portion. The resulting reaction mixture was stirred at room temperature for 36 h. Diluted with 5:1 etherpetane (100 ml) and washed with H_2O (50 ml), brine (50 ml). The combined organic phases were dried (Na_2SO_4), concentrated to give 8.4g (74%) of olefin.

To a solution of olefin (3.45g, 20 mmol) in CH_2Cl_2 (75 ml) was bulbed through a stream of ozone at -78°C until the blue color persisted. Excess ozone was removed by a stream of N_2, dimethyl sulfide (5 ml) was added, and the reaction mixture was allowed to warm to room temperature and stirred for 36 h. After removal of all solvents, the residue was dissolved in Et_2O (35 ml) and washed with H_2O (10 ml) and sat. NaCl solution (10 ml). The organic extracts were dried (Na_2SO_4), concentrated to afford 3.2g (92%) of ald hyde. To a s luti n of this aldehyde (3.2g, 18.4 mm l) in MeOH (80 ml) was added Na $CNBH_3$ (2.3g, 36.8 mm l) and acetic acid (2 ml) at 0°C. To this c ld s luti n was added morpholin (2g, 23 mmol)

slowly at 0°C and stirred for 2 h at 0°C, 16 h at room temp rature. The removal of solvents gav a solid, to this solid was added H_2O (20 ml) and Et_2O (50 ml). The organic layer was separated and to this was added 5% HCl (20 ml). The aqueous layer was collected and to this was added 2.5N NaOH solution until pH ~ 14, and extracted with Et_2O (25 ml x 3). The combined organic extracts were washed with brine (15 ml), dried (Na_2SO_4) and concentrated to afford 1.6g (35%) the desired amine. The amine (1.58g, 6.4 mmol) was subjected to a mixture of 10% NaOH (13 ml, 32 mmol) and MeOH (10 ml) and stirred for 16 h. Acetic acid (2.5 ml, 41.6 mmol) was added and the solvents were removed in vacuo to give a solid. The solid was washed with CH_2Cl_2 (25 ml x 4). The combined CH_2Cl_2 solutions were dried (Na_2SO_4) and concentrated to give an oil. The purification of the oil by plug filtration (silica gel, 20% MeOH/CH_2Cl_2 the MeOH) gave 350 mg (24%) pure amine acid as an oil.

Following generally the general procedure set forth below and the procedures set forth in Examples 1A and 2B, the compounds listed in Table 1 were prepared.

TABLE 1



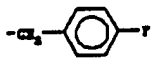
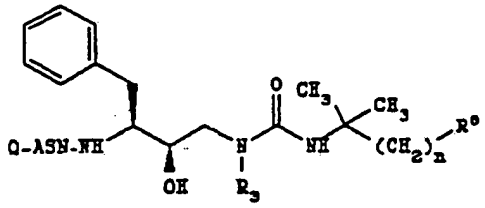
R^3	R^{16}	Method of Preparation
$-CH_2CH(CH_3)$	$-H$	Ex. 1
"	$-CH_3$	"
"	$-CH_2CH_3$	"
"	$-CH(CH_3)_2$	"
"	$-C(CH_3)_3$	Ex. 2
"	$-CH_2Ph$	Ex. 1
$-CH_2CH_2CH(CH_3)_2$	$-H$	Ex. 2
"	$-CH_3$	Ex. 1
"	$-C(CH_3)_3$	Ex. 2
	$-OH$	"
	$-CH_2CH_3$	"
	$-C(CH_3)_3$	"

TABLE 2



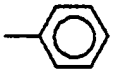
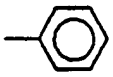
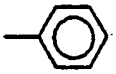
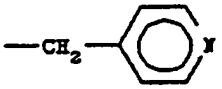
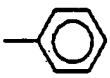
n	R^3	R^8	Method of Preparation
0	$-CH_2CH(CH_3)_2$	-CN	Ex. 1
0	$-CH_2CH_2CH(CH_3)_2$		Ex. 2
1	$-CH_2CH_2CH(CH_3)_2$		Ex. 2
1	$-CH_2CH_2CH(CH_3)_2$	$-C(O)N(CH_3)_2$	Ex. 2
1	$-CH_2CH_2CH(CH_3)_2$	$-CO_2CH_3$	Ex. 2
2	$-CH_2CH_2CH(CH_3)_2$		Ex. 2
1			Ex. 2

TABLE 2 (Cont'd)

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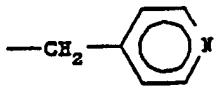
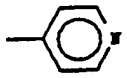
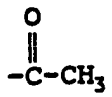
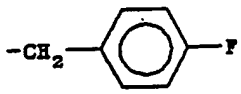
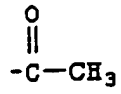
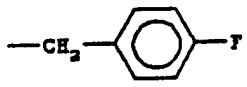
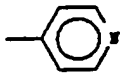
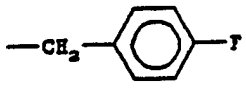
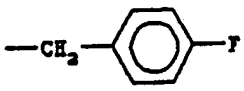
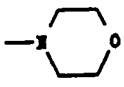
1			Ex. 2
0	$-CH_2CH_2CH(CH_3)_2$		Ex. 2
0			Ex. 2
1			Ex. 2
1	$-CH_2CH(CH_3)_2$	OH	Ex. 2
1		OH	Ex. 2
2			Ex. 2

TABLE 2 (Cont'd)

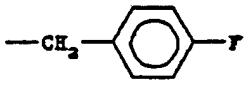
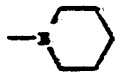
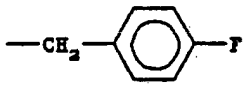
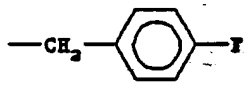
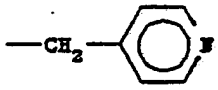
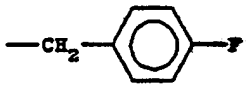
n	R^3	R^8	Method of Preparation
2			Ex. 2
1		$-SCH_3$	Ex. 2
1		$-SO_2CH_3$	Ex. 2
1		$-SO_2CH_3$	Ex. 2
1	$-CH_2CH(CH_3)_2$	$-CO_2CH_3$	Ex. 1
1		$-CO_2H$	Ex, 2

TABLE 2 (Cont'd)

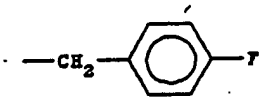
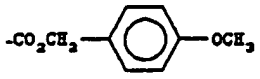
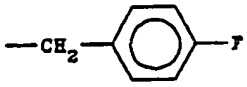
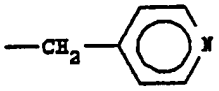
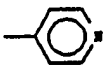
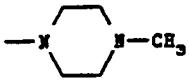
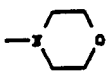
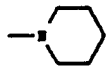
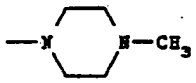
n	R^3	R^8	Method of Preparation
1			Ex. 2
1		$-SO_2Ph$	Ex. 2
1		$-SO_2Ph$	Ex. 2
1	$-CH_2CH_2CH(CH_3)_2$		Ex. 2
2	$-CH_2CH_2CH(CH_3)_2$	$-N(CH_3)_2$	Ex. 2
2	$-CH_2CH_2CH(CH_3)_2$		Ex. 2
1	$-CH_2CH_2CH(CH_3)_2$		Ex. 2

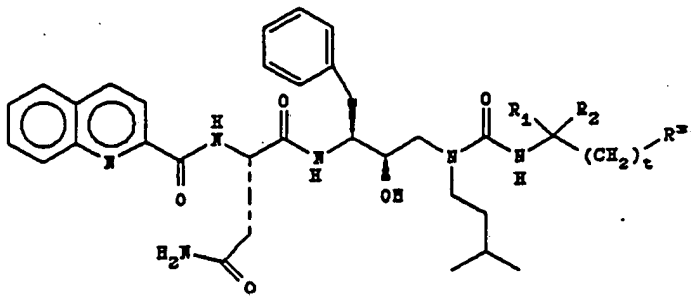
TABLE 2 (Cont'd)

n	R^3	R^8	Method of Preparation
1	$-CH_2CH_2CH(CH_3)_2$	$-N(CH_3)_2$	Ex. 2
1	$-CH_2CH_2CH(CH_3)_2$		Ex. 2
1	$-CH_2CH_2CH(CH_3)_2$		Ex. 2
1	$-CH_2CH_2CH(CH_3)_2$	$-N(CH_3)Ph$	Ex. 2

Example 3

Following generally the procedure of Examples 2A and B, the compounds shown in Table 3 were prepared.

TABLE 3

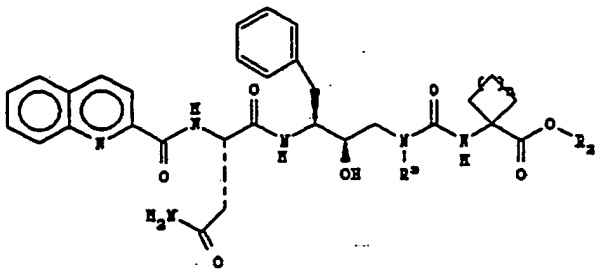


t	R_1	R_2	R	Method of Preparation
0	CH_3	$-CH_2CH_3$	$-C(O)OC(CH_3)_3$	Ex. 1
0	CH_3	CH_2Ph	$-C(O)OCH_2CH_3$	Ex. 1
1	R^1+R^2=cyclopentyl		4-pyridyl	Ex. 2
1	R^1+R=cyclobutyl		4-pyridyl	Ex. 2

Example 4

Following generally the procedure of Example 1, the compounds shown in Table 4 were prepared.

TABLE 4



n	R^3	R^{16}
0	isoamyl	CH_2CH_3
1	isoamyl	CH_2CH_3
2	isoamyl	CH_2CH_3
3	isoamyl	CH_2CH_3

Example 5

This example illustrates an alternate procedure for preparing compounds of Formula II.

A. Intermediates

Preparation of 2,2-Dimethyl-3-phenylpropionic Acid

To a mixture of 1.23g (41.0 mmol) of 80% sodium hydride and 50 mL of anhydrous tetrahydrofuran under a nitrogen atmosphere, was added 3.88g (38.3 mmol) of diisopropylamine and then 3.3g (37.5 mmol) of isobutyric acid. After heating at reflux for 15 minutes and cooling to 0°C, 15 mL (37.5 mmol) of 2.5M n-butyllithium in hexane was added. The mixture was warmed to 35°C for 30 min, cooled to 0°C and 6.40g (37.5 mmol) of benzyl bromide added. The mixture was stirred for 30 minutes at 0°C, th n warmed t0 35°C for one hour and reco led to 0°C. Water was added and the aqueous layer xtracted with diethyl th r, acidified with 6N aqueous HCl and

extracted with diethyl ether. The organic layer was dried and concentrated to provide 4.0g of crude product. Chromatography on silica gel using 10% methanol/methylene chloride afforded 1.0g of pure 2,2-dimethyl-3-phenylpropionic acid, m/e 185 (M + Li).

Preparation of 2,2-Dimethyl-3-(4-pyridyl)propionic Acid

Under a nitrogen atmosphere, 1.23g (41 mmol) of 80% sodium hydride was added to 50 mL of anhydrous tetrahydrofuran, followed by 3.88g (38.3 mmol) of diisopropylamine. To the resulting mixture was added 3.3g (37.5 mmol) of isobutyric acid and the resulting mixture heated to reflux for 15 minutes. Upon cooling to 0°C, 15 mL (37.5 mmol) of 2.5M n-butyllithium in hexane was added and the mixture then warmed to 35°C for 30 minutes. After cooling to 0°C, 4.8g (37.5 mmol) of 4-chloromethylpyridine (freshly prepared by neutralization of the hydrochloride salt with aqueous sodium bicarbonate, extraction with hexane, dried and concentrated) was added. After 30 minutes at 0°C, the mixture wa warmed to 30°C for one hour, cooled to 0°C and 50 mL of water carefully added. The aqueous layer was separated and washed twice with diethyl ether, acidified with 6N aqueous hydrochloric acid, rewashed twice with diethyl ether and then neutralized with aqueous sodium bicarbonate. After the addition of citric acid, the aqueous layer was extracted 3 xs with ethyl acetate to afford 283 mg of a white powder which was identified as 2,2-dimethyl-3-(4-pyridyl)propionic acid, m/e 180 ($M + H^+$).

Preparation of 1-(4-Pyridylmethyl)cyclopentanecarboxylic Acid

To a suspension of 3.69g (123 mmol) of 80% sodium hydride in 150 mL of anhydrous tetrahydr -furan and 11.6g (115 mmol) of diisopropylamine, at 0°C was added 12.82g (112 mm l) of cyclo-p ntan carboxylic acid. This was then heated at reflux for 15 minutes, co led to 0°C

and 45 mL of 2.5M n-butyllithium in hexan added. After 15 minutes at 0°C and 30 minutes at 35°C, the mixture was recooled to 0°C and a solution of 14.4g (112 mmol) of 4-chloromethylpyridine (freshly prepared from 4-chloromethylpyridine hydrochloride by neutralization with aqueous sodium bicarbonate, extraction with hexane, drying and concentrating) was added. After 30 minutes at 0°C and 60 minutes at 35°C, the mixture was cooled to 0°C, water carefully added and extracted twice with diethyl ether. The aqueous layer was acidified to pH3 with 6N hydrochloric acid whereupon a precipitate formed. The pH was adjusted to 5.9 with 10% sodium hydroxide and the solids collected. Recrystallization from hot ethanol and hexane afforded 5.7g of desired product, m/e 206 (M + H).

Preparation of 2,2-Dimethyl-3-(methylsulfonyl)propionic Acid.

To a suspension of 1.23g (41 mmol) of 80% sodium hydride in 50 mL of anhydrous tetrahydrofuran and 3.88g (38 mmol) of diisopropylamine, was added 3.3g (37 mmol) of isobutyric acid and the mixture refluxed for 30 minutes. Upon cooling to 0°C, 15 mL (37 mmol) of 2.5M n-butyllithium in hexane was added, stirred for 15 minutes at 0°C and then warmed to 35°C for 45 minutes. After cooling to 0°C, 3.62g (37 mmol) of chloromethyl methyl sulfide was added and stirred for 30 minutes at 0°C and then 60 minutes at 35°C. After cooling to 0°C, waster was added, washed with diethyl ether, acidified with 6N hydrochloric acid and extracted with diethyl ether, dried and concentrated to afford 4g of crude material. This was distilled (Bp 85°C, 0.25 mm Hg) to afford 1.2g of 2,2-dimethyl-3-(thiomethyl)propionic acid, m/e 155 (M + Li). To a solution of 525 mg (3.5 mmol) of 2,2-dimethyl-3-(thi methyl)propionic acid in 8 mL of acetic acid was added 1.2 mL of 30% aque us hydrogen peroxide and the mixture refluxed for 2 hours. The solution was c oled, 15 mL of 10% sodium sulfite added and

concentrated under reduced pressure. The residue was acidified with 12N hydrochloric acid, extracted with ethyl acetate, washed with brine, dried and concentrated to afford 341 mg of 2,2-dimethyl-3-(methylsulfonyl)-propionic acid.

Preparation of 2,2-Dimethyl-3-(phenylsulfonyl)propionic Acid.

To a mixture of 1.23g (41 mmol) of 80% sodium hydride in 50 mL of dry tetrahydrofuran was added 3.88g (38.3 mmol) of diisopropylamine and then 3.3g (37.5 mmol) of isobutyric acid. After heating at reflux for 15 min, and cooling to 0°C, 15 mL (37.5 mmol) of a 2.5M n-butyllithium in hexane solution was added over 10 min. After 15 min, the solution was heated to 35°C for 30 min, cooled to 0°C and 5.94g (37.5 mmol) of chloromethylphenyl sulfide was added. After 30 min at 0°C and 35°C for 1 hour, the solution was recooled to 0°C, water added and then diethyl ether. The water layer was separated, acidified and extracted with diethyl ether, dried and concentrated to afford 4.23g of crude product. Recrystallization from methylene chloride/hexane afforded 1.49g of 2,2-dimethyl-3-(thiophenyl)propionic acid, m/e 211 (M + H).

To a mixture of 1.1g (5.2 mmol) of 2,2-dimethyl-3-(thiophenyl)propionic acid in 12 mL of acetic acid was added 1.8 mL (17.8 mmol) of 30% aqueous hydrogen peroxide. After 10 minutes at room temperature, all the solids dissolved and the solution was heated to reflux for two hours. After cooling in an ice bath, 23 mL of 10% aqueous sodium sulfite was added and the volatiles removed under vacuum. The residue was acidified with 12N aqueous HCl, extracted with ethyl acetate, dried and concentrated to afford 1.23g of 2,2-dimethyl-3-(phenylsulfonyl)propionic acid, m/e 260 ($M + NH_4^+$).

B. Compounds of the Invention

I. Preparation of Butanediamide, N^1-[3-[[[(1'1-dimethyl-2-phenylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [1S-[1R*(R*), 2S*]]-

To a solution of 72 mg (0.40 mmol) of 2,2-dimethyl-3-phenylpropionic acid in 5 mL of toluene and 0.12g (1.2 mmol) of triethylamine at 90°C, was added 0.11g (0.40 mmol) of diphenylphosphoryl azide. After one hour, a solution of 208 mg (0.40 mmol) of N-3(S)-[N-(2-quinolinylcarbonyl)-L-asparaginyl]amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl) in 1.5 mL of N,N-dimethylformamide was added. After one hour, the solvent was removed under reduced pressure, ethyl acetate added, washed with water, sat d sodium bicarbonate, sat d sodium chloride, dried, filtered and concentrated to afford 200 mg of crude product. This was recrystallized from ethyl acetate and hexane to afford 42 mg of the desired product, m/e 701 (M + Li).

II. Preparation of Butanediamide, N^1-[3-[[[(1,1-dimethyl-2-(4-pyridyl)ethyl)amino]carbonyl](3-(4-fluorophenyl)methyl)amino]-2-hydroxy-1-(phenylmethyl)propyl-2-[(2-quinolinylcarbonyl)amino],-[1S-[1R*(R*), 2S*]]-

To a solution of 96 mg (0.54 mmol) of 2,2-dimethyl-3-(4-pyridyl)propionic acid in 5 mL of toluene and 0.16g (1.62 mmol) of triethylamine at 95°C, was added 149 mg (0.54 mmol) of diphenylphosphoryl azide. After one hour, a solution of 300 mg (0.54 mmol) of N-3(S)-[N-(2-quinolinylcarbonyhl)-L-asparaginyl]amino-2(R)-hydroxy-4-ph nylbutylamine, N-(4-flu rophenyl)-methyl in 2 mL of N,N-dimethylf rmamide was added.. After on hour, the s lvents were rem ved under reduced pressure, ethyl

ac tate added, washed with water, sat d s dium bicarbonate, brine, dried, filt red and concentrated to afford 320 mg of crude product. Chromatography on silica gel using 5-30% isopropanol/methylene chloride afforded 60 mg of the desired product, m/e 734 (M + H).

III. Preparation of Butanediamide, N -[3-[[[(1,1-dimethy-2-hydroxyethyl)amino]carbonyl](4-fluoro-phenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-[1S-[1R*(R*), 2S*]]-

To a solution of mono-tertiary-butyl 2,2-dimethylmalonate (188 mg, 1.0 mmol), Et_3N (303 mg, 3.0 mmol) in toluene (2 ml) was added DPPA (283 mg, 1.0 mmol) in toluene (0.5 ml) dropwise over 5 min at 95° (oil bath). After stirring at 95°C (oil bath) for another 45 min, the mixture was cooled to r.t. and to this was added a solution of free amine (588 mg, 1.0 mmol) in DMF (5 ml) and stirred at r.t. for 45 min. The mixture diluted with EtOAc (25 ml) and washed with 5% $NaHCO_3$ (10 ml x 2), 5% citric acid (5 ml) and H_2O (10 ml) then sat. NaCl (10 ml). The organic phase was dried (Na_2SO_4) and concentrated to afford 840 mg crude product. Purification of crude product by flash chromatography (silica gel, 3% then 5% MeOH/CH_2Cl_2) afforded 568 mg (76%) of pure desired product as a white solid, m/e 749 (M + Li). This white solid (520 mg, 0.699 mmol) was dissolved in CH_2Cl_2 (3 ml) and to this was added TFA (1.5 ml). After the mixture was stirred at r.t. for 16 h, the solvents were removed in vacuo to afford 475 mg (98%) of acid as a white solid. This white solid (450 mg, 0.65 mmol) was dissolved in THF (3 ml) and cooled to 0°C. To this cold solution was added $BH_3 \cdot Me_2S$ (0.3 ml of 10 M solution, 3 mmol) dropwise via a syring . After the mixture was stirred at 0°C for another 1 h and at r.t. f r 16 h, it was qu nched with M OH (1 ml). The solvents were removed in vacu and MeOH (2 ml) was added and stripped off again. This

procedur was repeated for 3 more times. A white solid was obtained. Purification of the crude product by flash chromatography (silica gel, 10% MeOH/.CH_2Cl_2) gave 108 mg (25%) of pure alcohol as a white solid, m/e 679 (M + Li).

IV. Preparation of Butanediamide, N -[3-[[[3-(3,3-dimethylpropionic acid, dimethyl amide)amino]-carbonyl](4-fluorophenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [1S-[1R*(R*), 2S*]]-

Part A. Preparation of 2,2-Dimethylsuccinic acid, 4-(mono-para-methoxybenzyl ester).

A 250 ml RB flask equipped with magnetic stir bar, reflux condensor and N_2 inlet was charged with 5.0g (39 mmol) of 2,2-dimethyl succinic anhydride, 5.39g (39 mmol) of p-methoxy benzyl alcohol (MOS-OH) in 65 ml toluene. After overnight reflux the reaction mixture was concentrated in vacuo and triturated with hexane to yield 9.1g crude solid: 6:1 mixture of regioisomers. After washing with hexane the crude solid was recrystallized from 85 ml boiling hexane to yield 5.9g (57%) of white solid. Regioisomeric purity was >25:1 by 400 MHz ^{1}H-NMR.

Part B. Preparation of Butanediamide, N -[3-[[[3-(3,3-dimethyl propionic acid, 4-methoxy-phenylmethyl ester)amino]carbonyl](4-fluorophenymethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-[1S-[1R*(R*), 2S*]]-.

A 100 ml RB flask equipped with magnetic stir bar, reflux condensor and N_2 inlet was charged with 120 mg (.45 mmol) of product from Part A, 189 µl (1.35 mmol) NEt_3 in 5 ml dry toluene. The reaction was stirred at 95°C while 125 ml (.45 mmol) DPPA was slowly added. After 1 hour the free amine A : 250 mg (.45 mmol), pre-dissolved in 4 ml DMF, was added. Aft r 1 hour the

r action was concentrated in vacuo and partioned between EA and 5% aq citric acid. Organics washed with H_2O, sat bicarb, brine and dried over Na_2SO_4. Concentration in vacuo yielded 440 mg crude foam. Flash chromatography (100% EA) yielded 270 mg (73%) solid. Pure by ^1H-NMR and FAB mass spec (M + H = 822).

Part C. Preparation of Butanediamide, N -[3-[[[3-(3,3-dimethylpropionic acid)amino]carbonyl]-(4-fluorophenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)-amino]-,[1S-[1R*(R*), 2S*]]-.

A 100 liter RB flask equipped with magnetic stir bar and N_2 inlet was charged with 260 mg (.32 mmol) 2 in 20 ml 4N HCl/dioxane. The homogeneous solution was stirred at RT 30 min then to 50°C for 30 min. The reaction mixture was concentrated in vacuo to yield an oily solid that was titurated from excess Et_2O, filtered and dried to yield 150 mg (68%) of white powder suitable for use without further purification. FAB mass spec gave gave M + H = 702, M + Li = 708.

Part D. Preparation of Butanediamide, N -[3-[[[3-(3,3-dimethylpropionic acid, dimethyl amide)amino]-carbonyl](4-fluorophenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [1S-[1R*(R*), 2S*]]-.

A 25 ml RB flask equipped with magnetic stir bar and N_2 inlet was charged with 50 mg (.07 mmol) acid in 1 ml DMF. The reaction was cooled to 0°C when 15 mg HOBt (.11 mmol) was added followed by 15 mg (.08 mmol) EDCI. After stirring 20 minutes 50 ml 40% aq. dimethyl amine was added. The reaction was stirred 2 h urs @ 0°C and allow d to stir at room t mperatur vernight. The reacti n was taken up in EA and wash d with 2x20 µl sat. bicarb, 2x20 ml 5% aq citric acid, 1x30 ml brine, and

over $MgSO_4$. Conc ntration in vacuo yield 21 mg crude solid TLC (5% MeOH-CH_2Cl_2). Showed 50% conversion to product with other impurities. Flash chromatography (MeOH-CH_2Cl_2) yield 6.5 mg product (13%). Mass spec M + H = 728.

Preparation of Butanediamide, N -[3-[[[(1,1-dimethyl-2-oxo-propyl)amino]carbonyl](2-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [1S-[1R*(R*), 2S*]]-

Part A. Preparation of Methyl 2,2-Dimethyl-3-oxobutyric Acid.

A 250 ml RB flask equipped with magnetic stir bar, addition funnel and N_2 inlet was charged with 8.9g of 95% NaH (372 mmol, 2.2 eq) and 125 ml dry THF. The slurry was cooled to -30°C when 20g (170 mmol) of methyl acetoacetate was slowly added. After 5 min 51g (359 mmol, 2.1 eq) of methyl iodide was added and the reaction was stirred 1 hour at -25°C and allowed to sit at room temperature overnight. Upon workup the reaction was diluted with 125 ml EA and the precipated sodium iodide was filtered and the filtrate was washed with 100 ml sat. bicarb, 100 ml 5% aq $Na_2S_2O_5$ and 100 ml brine. The organics were dried and concentrated in vacuo to yield 19g of a yellow oil suitable for use without further purification.

Part B. Synthesis of 2,2-Dimethyl-3-oxobutyric acid, ethylene glycol Keml Dicyclohexyl-ammonium Salt.

A 100 ml RB flask equipped with magnetic stir bar and N_2 inlet was charged with 5g (34.7 mmol) 2,2-dimethyl methylacetoacetate in 25 ml anhydrous ethylene glycol, 20 ml trimethyl rthoformate with a catalytic amount of p-toluenesulf nic acid. The reaction mixture was stirred @ 55°C overnight then worked up by pouring into 200 ml 20% aq KOH and heating t 95°C f r 4 hours. The c ol d reaction mixture was extracted with ether and the

aqueous phase was acidified to pH 3 with 35 ml conc HCl/ice. The product was extracted with 2x100 ml EA. The organics were dried over Na_2SO_4 and concentrat d in vacuo to ~ 5g crude free acid.

The acid was taken up in 50 ml ether and 5.3g dicyclohexyl amine salt was added and the product was filtered and dried to yield 6.5g (~ 53%) white solid. Mp 124-127°C.

Part C. Preparation of N^3-3(S)-(Benzyloxycarbonyl)amino-2-(R)-hydroxy-4-pentylbutyl amine, N -(3-methyl)butyl, N -[[(1,1-dimethyl-2-oxo-propyl)amino]carbonyl, ethylene glycol ketal].

A 250 ml RBF equipped with magnetic stir bar and N_2 inlet was charged with 2.0g (11.5 mmol) free acid: free acid liberated from DCHA salt by partioning between Et_2O and 5% aq $KHSO_4$, 6.11 ml (43.7 mmol - 3.8 eq) NEt_3 in 75 ml dry toluene. The solution was heated to 95°C and 3.16g (11.7 mmol) DPPA was added. The reaction was stirred at 95°C for 1 hour when 4g (11.7 mmol) A in 50 ml toluene was added. The reaction was stirred at 90°C for 1 hour than at room temperature overnight. The reaction was concentrated in vacuo and partionned between EA and 5% aq citric acid. The organic phase was washed with sat. bicarb, brine, dried, and concentrated to 6g of crude foam. The product was purified by flash chromatography on silica gel to yield 4.3g (73%) white foam, pure by TLC and high field NMR. FAB mass spec, M + Li = 562 z/m.

Part D. Preparation of butanediamide, N -[3-[[[(1,1-dimethyl-2-oxo-propyl)amino]carbonyl](2-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quin linylcarb nyl)amino]-, [1S-[1R*(R*), 2S*]]-. A Fish r P rter tube equipp d with magn tic stir bar was charg d with 1.5g of pr duct from Part C, 45 mL of methanol and a catalytic am unt of 10% Pd-C. The

mixture was hydrogenated at 45 psi for 20 hours. The reaction was filtered through celite and concentrated in vacuo to yield 1.1g (>95%) of free amine, which was used without further purification.

A 100 ml RBF equipped with magnetic stir bar and N_2 inlet was charged with 824 mg (3.14 mmol, 1.15 eq) Z-asparagine in 100 ml DMF. The solution was cooled to 0°C and 550 mg (4.07 mmol, 1.5 eq) HOBt was added followed by 60 mg (3.13 mmol, 1.15 eq) EDCI. The reaction was stirred 10 minutes when 1.13g (2.7 mmol) crude free amine was added. The reaction was stirred 1 hour at 0°C then overnight at room temperature. The reaction was poured into 100 ml sat. bicarb and extracted with 100 ml EA. The organics were washed with 5% citric acid, brine, dried over Na_2SO_4, and concentrated in vacuo to yield 1.37g (75%) white solid which was identified as the CBZ-asparagine adduct. FAB mass spec gave M + Li 676 z/m.

A Fisher Porter tube equipped with magnetic stir bar was charged with 1.37g of CBZ-asparagine adduct, 50 mL MeOH and a catalytic amount of 10% Pd-C. The reaction mixture was hydrogenated at 50 psi for 16 hours. The reaction was filtered through celite and concentrated in vacuo to yield 1.05g (97%) of free asparagine amine as a foam that was used without further purification. FAB mass spec gave M + Li = 542.

A 100 ml RBF equipped with magnetic stir bar and N_2 inlet was charged with 356 mg (2.06 mmol, 1 eq) 2-quinaldic acid in 10 ml dry DMF. The solution was cooled to 0°C and 415 mg (3.07 mmol, 1.5 eq) HOBt was added followed by 415 mg EDCI (2.16 mmol, 1.05 eq). The r action was stirred 2 hours at 0°C when 1.1g (2.06 mm l, 1 eq) f free asparagine amine in 10 ml dry DMF was add d. The reacti n was stirred at 0°C for 2 hours then r om temperature vernight. The reaction was poured into sat. bicarb and extracted with 2x65 mL thyl

acetate. The combined organics were washed with 5% aq. citric acid, brine, dried and concentrated to 1.4g crude foam. Purification by flash chromatography on silica gel (100% EA) yielded 850 mg (61%) of quinoline adduct.

A 100 ml RBF equipped with magnetic stir bar was charged with 117 mg quinoline Ketal, 30 ml of THF and 15 ml 30% aq HCl. The reaction was stirred 2 hours at room temperature then diluted with 50 ml EA. The organic phase was washed with sat. bicarb, brine, dried and concentrated in vacuo to 105 mg pure ketone. FAB mass spec gave M + Li at 653 z/mol.

Preparation of Butanediamide, N -[3-[[[(1,1-dimethyl-2-oxo-propyl)amino]carbonyl](2-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [1S-[1R*(R*), 2S*]]-.

To a solution of 0.22g of 2(S)-methyl-3-(methylsulfonyl)propionic acid, 0.29g of N-hydroxybenzotriazole in 5 mL of N,N-dimethylformamide at 0°C was added 0.31g of EDCI. After 30 minutes, a solution of 3-[[[1,1-dimethyl-2-(4-pyridyl)ethyl]amino]carbonyl](3-methylbutyl)amino-2-(R)-hydroxy-1(S)-(phenylmethyl)propyl amine in 2 mL N,N-dimethylformamide was added and the solution stirred for 17 hours at room temperature, poured into saturated aqueous bicarbonate, chilled and filtered, and the solids washed with aqueous bicarbonate and water. The resulting solids were dissolved in methyhlene chloride, washed with aqueous bicarbonate, brine, dried, filtered and concentrated to afford 160 mg of the desired product.

Preparation of butanediamide, N -[3-[[[[1,1-dimethyl-2-(4-morpholinyl)ethyl]amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-,[1S-[1R*(R*), 2S*]-.

Dissolve 90.40 mg (0.4 mmoles, 1.05 eq.) amino acid (3) in toluene. Heat to 95 degrees C. under N_2. Add 225µl (1.61mmoles, 4.2 eq.) triethylamine. Slowly add 87.1µl (0.4 mmoles, 1.05eq.) diphenylphosphoryl azide. Stir 1 hour. To this solution add 200 mg (0.38 mmoles, 1 eq.) 3(S)-[N-(2-quinolinylcarbonyl)-L-asparaginyl]amino-2(R)-hydroxy-4-phenylbutyl amine, N-(3-methylbutyl) dissolved in DMF. Stir 1 hour. Cool to room temperature. Strip off toluene. Dissolve in EtOAc. Wash 1xH_2O, 1x saturated $NaHCO_3$, 1x saturated NaCl. Dry with $MgSO_4$ and rotovap. Purify by silica flash chromatography (30:1 CH_2Cl_2:CH_3OH) Yield=50% M+H=704

Preparation of butanediamide, N -[3-[[[[1,1-dimethyl-3-(4-(1-methylpiperazinyl))propyl]amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-, [1S-[1R*(R*), 2S*]-.

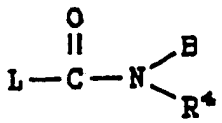
Dissolve 122.2 mg (0.57 mmoles, 1.5 eq.) amino acid of 2,2-dimethyl-4-(1-(4-methylpiperazinyl))butanoic acid in toluene. Heat to 95 degrees C. under N_2. Add 238µl (1.71mmoles, 4.5 eq.) triethylamine. Slowly add 122.8µl (0.57 mmoles, 1.5eq.) diphenylphosphoryl azide. Stir 1 hour. To this solution add 200 mg (0.38 mmoles, 1 eq.) 3(S)-[N-(2-quinolinylcarbonyl)-L-asparaginyl]amino-2(R)-hydroxy-4-phenylbutyl amine, N-(3-methylbutyl) dissolved in DMF. Stir 1 hour. Cool to room temperature. Strip off toluene. Dissolve in EtOAc. Wash 1xH_2O, 1x saturated $NaHCO_3$, 1x saturated NaCl. Dry with $MgSO_4$ and rotovap. Purify by recrystalizing in EtOAc/pet. ether. Yield=66% M+Li=737

Preparation of butanediamide, N-[3-[[[[(1,1-dimethyl-5-(4-morpholinyl)-3-oxapentyl]-amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quin linyl-carbonyl)amino]-, [1S-[1R*(R*), 2S*]-.

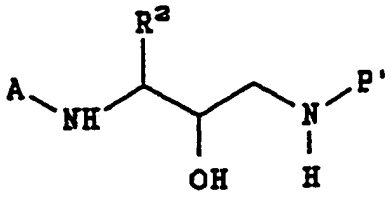
To a mixture of acid 10 (231 mg, 1.0 mmol) EtN_3 (303 mg, 3.0 mmol) in toluene (2 ml) was added DPPA (283 mg, 1.0

mmol) in toluene (0.5 ml) dropwise over 5 min at 95°C (il bath). After stirring at 95°C (oil bath) for another 45 min, the mixture was cooled to room temperature and to this was added a solution of 3(S)-[N-(2-quinolinylcarbonyl)-L-asparaginyl]amino-2(R)-hydroxy-4-phenylbutyl amine, N-(3-methylbutyl) (519.6 mg, 1.0 mmol) in DMF (5 ml) and stirred at room temperature for 45 min. The mixture was diluted with EtOAc (25 ml) and washed with 5% $NaHCO_3$ (10 ml x 2), 5% citric acid (5 ml and H_2O (10 ml) then sat. NaCl solution (10 ml). The combined extracts were dried (Na_2SO_4) and concentrated to give a solid. The purification of the crude product by flash chromatography (silica gel, 3% MeOH/CH_2Cl_2) gave 262 mg (35%) pure product.

The above procedures could be utilized to prepare compounds of the present invention wherein the group B as defined above is incorporated into the compound shown below in Examples 6-36. It is contemplated that the resulting compounds would inhibit retroviral proteases with activities similar to the activities of the compounds of Examples 1-5. Thus, a compound of the formula



can be utilized in place of the isocyanate of Step D of Example 1. Alternatively, the compounds represented by the formula:



can be prepared and, following deprotection, can be reacted with the above compound as in Example 5.

Example 6A

Preparation of [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino] -2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide

Part A:

To a solution of 75.0g (0.226 mol) of N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of tetrahydrofuran at -2°C, was added 13.17g (0.348 mol, 1.54 equiv.) of solid sodium borohydride over one hundred minutes. The solvents were removed under reduced pressure at 40°C and the residue dissolved in ethyl acetate (approx. 1L). The solution was washed sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and then saturated sodium chloride solutions. After drying over anhydrous magnesium sulfate and filtering, the solution was removed under reduced pressure. To the resulting oil was added hexane (approx. 1L) and the mixture warmed to 60°C with swirling. After cooling to room temperature, the solids were collected and washed with 2L of hexane. The resulting solid was recrystallized from hot ethyl acetate and hexane to afford 32.3g (43% yield) of N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp 150-151°C and $M+Li^+$ = 340.

Part B:

To a solution of 6.52g (0.116 mol, 1.2 equiv.) of potassium hydroxide in 968 mL of absolute ethanol at room temperature, was added 32.3g (0.097 mol) of N-CBZ-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After stirring for fifteen minutes, the solvent was removed under reduced pressure and the solids dissolved in methylene chl ride. Aft r washing with water, drying over magnesium sulfate, filtering and stripping, ne obtains 27.9g f a white solid. Recrystallization from

h t thyl acetat and hexane afforded 22.3g (77% yield) of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane, mp 102-103°C and MH^+ 298.

Part C:

A solution of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane (1.00g, 3.36 mmol) and isobutylamine (4.90g, 67.2 mmol, 20 equiv.) in 10 mL of isopropyl alcohol was heated to reflux for 1.5 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 100 mL of stirring hexane whereupon the product crystallized from solution. The product was isolated by filtration and air dried to give 1.18g, 95% of N=[[3(S)-phenylmethylcarbamoyl)amino-2(R)-hydroxy-4-phenylbutyl]N-[(2-methylpropyl)]amine mp 108.0-109.5°C, MH^+ m/z = 371.

Part D:

A solution of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenylbutyl]N-[(2-methylpropyl)]amine in 10 ml of tetrahydrofuran was treated with tert-butylisocyanate (267 mg, 2.70 mmol) at room temperature for 5 minutes. The solvent was removed in vacuo and replaced with ethyl acetate. The ethyl acetate solution was washed with 5% citric acid, water, and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to give 1.19g, 97% of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenyl]-1-[(2-methylpropyl)]amino-2-(1,1-dimethyl)amino]carbonyl]butane, MH^+ m/z = 470.

Part E:

A solution of (1.00g, 2.21 mmol) [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenyl]-1-[(2-methylpropyl)]amino-1-(1,1-dimethylethyl)amino]carbonyl]butane in 2 mL f methanol was hydrog nated over 10% palladium-on-carbon for 4 hours to give [2(R), 3(S)]-N-[[3-amino]-2-hydroxy-4-phenyl]-1-[(2-methylpropyl)amino-1-(1,1-dim thylethyl)amino]carbonyl]butane 720 mg, 97%.

Part F:

A solution of N-Cbz-L-asparagine (602mg, 2.26 mmol) and N-hydroxybenzotriazole (493 mg, 3.22 mmol) in 2mL of dimethylformamide was cooled to 0°C and treated with EDC (473 mg, 2.47 mmol). The solution was allowed to stir at 0°C for 20 minutes and then treated with [2(R), 3(S)]-N-[[3-amino]-2-hydroxy-4-phenyl]-1-[(2-methylpropyl)]amino-1-(1,1-dimethylethyl)amino]carbonyl]butane (720 mg, 2.15 mmol) in 1mL of dimethylformamide. The solution was allowed to warm to room temperature and held at this temperature for 7 hours. The reaction mixture was then poured into 100 mL of 60% saturated aqueous sodium bicarbonate whereupon a white precipitate formed that was isolated by filtration. The filter cake was washed with water, 5% aqueous citric acid, water and then dried in vacuo to give 1.04g, 83% of [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino], mp. 164.0-166.5°C, MH^+ m/z = 584.

Part G.

A solution of [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(phenylmethylcarbamoyl)amino]-butanediamide (1.00g, 1.72 mmol) in 10 mL of methanol was hydrogenated over 10% palladium-on-carbon for 4 hours to give [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-amino]-butanediamide, 784mg, 99%.

Part H:

A mixture of [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpr pyl)amino]-2-hydr xy-1-(phenylm thyl)propyl]-2-amino]-butanediamide, (784 mg, 1.70 mmol), 2-quinoline carb xylic acid N-hydr xysuccinimid ester (459 mg, 1.70 mm l), N-m thylmorph line (343 mg, 3.40 mmol) in 5 mL of dichloromethane was stirred at room

temperature for 15 minutes. The solvent was removed in vacuo and replaced with ethyl acetate and the solution washed with 5% aqueous citric acid, saturated aqueous sodium bicarbonate, brine, dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product was recrystallized from acetone/hexane to give 790 mg, 77% of [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide, mp 107.0-109.8°C, MH^+ = 605.

Example 6B

The procedure described in Example 1, part C-H, was used to prepare [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide.

a) From the reaction of 1.06g (3.56mmol) of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane and 6.25g (71.7mmol) of isoamylamine, one obtains 1.27g (92%) of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine, mp 130-132C and MH* 385. This amine (400mg, 1.04mmol) was then reacted with tert-butylisocyanate (110mg, 1.11mmol) to afford 500mg (100%) of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenyl]-1-[(3-methylbutyl)]amino-1-(1,1-dimethylethy)amino]carbonyl]butane; as an oil, MH^+ 484.

b) The CBZ protected compound (530mg, 1.10mmol) was then deprotected by hydrogenation over 10% palladium-on-carbon and the resulting free amine c upled with N-CBZ-L-asparagine (377mg, 1.42mm l) in the presence f N-hydr xybenzotriazole (290mg, 2.15mm l) and EDC (300mg, 1.56mmol) t yield 430mg (53%) f [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dim thylethyl)amino]carbonyl](3-methylbutyl)amino]-

2-hydroxy-1-(phenylmethyl)propyl]-2-[(phenylmethylcarbamoyl)amino]-butanediamide, mp 148-151 C (dec) and MH^+ 598. This compound (370mg, 0.619mmol) was then deprotected by hydrogenation over 10% palladium-on-carbon and the resulting free amine coupled with 2-quinolinecarboxylic acid N-hydroxy-succinimide ester (193mg, 0.714mmol), in the presence of N-methylmorpholine, to afford 310mg (70%) of pure [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide; mp 93.5-95.5C and MH^+ 619.

Example 6C

The procedure described in Example 1, part C-H, was used to prepare [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl]2-napthylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amio]-butanediamide.

a) From the reaction of 1.80g (6.05mmol) of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane and 1.15g (7.31mmol) of 2-(aminomethyl)naphthalene, one obtains 2.11g (77%) of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenylbutyl]N-[(2-napthylmethyl)]amine, MH^+ 455. This amine (366.8mg, 0.807mmol) was then reacted with tert-butylisocyanate (66.4mg, 0.67mmol) to afford 350.0mg (94%) of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenyl]-1-[(2-napthylmethyl)]amino-1-(1,1-dimethylethyl)amino]carbonyl]butane; as an oil, MH^+ 554.

b) The CBZ protected compound (330mg, 0.596mmol) was then deprotected by hydrogenation over 10% palladium-on-carbon and the resulting free amine coupled with N-CBZ-L-asparagine (165.1mg, 0.62mmol) in the presence of N-hydroxybenzotriazole (142.3mg, 0.93mmol) and EDC (130.7mg, 0.68mmol) to yield

161.7mg (41%) of [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-napthylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(phenylmethylcarbamoyl)amino]-butanediamide; mp 151-152 C (dec) and MH^+ 668. This compound (91.0mg, 0.136mmol) was then deprotected by hydrogenation over 10% palladium-on-carbon and the resulting free amine coupled with 2-quinolinecarboxylic acid N-hydroxysuccinimide ester (36.8mg, 0.136mmol), in the presence of N-methylmorpholine, to afford 65.8mg (70%) of pure [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-napthylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide; mp 119-120C and MH^+ 689.

Example 6D

The procedure described in Example 1, part C-H, was used to prepare [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2-phenylethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide.

a) From the reaction of 1.00g (3.36mmol) of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane and 8.19g (67.0mmol) of 2-phenethyl amine, one obtains 1.10g (79%) of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenylbutyl]N-[(2-phenylethyl)]amine, mp 137-138 C and MH^+ 419. This amine (750mg, 1.79mmol) was then reacted with tert-butylisocyanate (178mg, 1.79mmol) to afford 897mg (97%) of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenyl]-1-[(2-phenylethyl)]amino-1-(1,1-dimethyl thyl)amino]carbonyl]butane; as an oil, MH^+ 518.

b) The CBZ protected compound (897mg, 1.73mmol) was then deprotected by hydrogenation over 10%

palladium-on-carbon and the resulting free amine coupled with N-CBZ-L-asparagine (620.7mg, 2.33mmol) in the presence of N-hydroxybenzotriazole (509.5mg, 3.33mmol) and EDC (488.0mg, 2.55mmol) to yield 1.00g (92%) of [1S-[1R*(R*), 2S*]]- N^1[3[[[(1,1-dimethylethyl)amino]carbonyl](2-phenylethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(phenylmethylcarbamoyl)amino]-butanediamide; mp 145 (dec) and MH^+ 632. This compound (860mg, 1.36mmol) was then deprotected by hydrogenation over 10% palladium-on-carbon and the resulting free amine coupled with 2-quinolinecarboxylic acid N-hydroxysuccinimide ester (338mg, 1.25mmol), in the presence of N-methylmorpholine, to afford 450.4mg (55%) of pure [1S-[1R*(R*), 2S*]]- N^1[3[[[(1,1-dimethylethyl)amino]carbonyl](2-phenylethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide; mp 139-140°C and MH^+ 653.

Example 6E

The procedure described in Example 1, part C-H, was used to prepare [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2,2-dimethylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide.

a) From the reaction of 1.00g (3.36mmol) of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane and 7.9mL (approx. 67mmol) of neopentyl amine, one obtains 0.69g (49%) of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenylbutyl]N-[(2,2-dimethylpropyl)]amine, MH^+ 385. This amine (686mg, 1.78mmol) was then reacted with tert-butylis cyanate (180mg, 1.78mmol) to afford 860mg (100%) f [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amin]-2-hydr xy-4-phenyl]-1-[(2,2-dimethylpropyl)]amino-1-(1,1-dimethylethyl)amino]carbonyl]butane; MH^+ 484.

b) The CBZ protected compound (860mg, 1.78mmol) was then deprotect d by hydrogenation over 10% palladium-on-carbon and the resulting free amine coupled with N-CBZ-L-asparagine (471mg, 1.77mmol) in the presence of N-hydroxybenzotriazole (406mg, 2.66mmol) and EDC (374mg, 1.95mmol) to yield 326mg (34%) of [1S-[R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2,2-dimethylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(phenylmethylcarbamoyl)amino]-butanediamide; mp 177-178C and MH^+ 598. This compound (245mg, 0.41mmol) was then deprotected by hydrogenation over 10% palladium-on-carbon and the resulting free amine coupled with 2-quinolinecarboxylic acid N-hydroxy-succinimide ester (111mg, 0.41mmol), in the presence of N-methylmorpholine, to afford 150mg (59%) of pure [1S-[R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](2,2-dimethylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide; mp 115-117C and MH^+ 619.

The procedure described in Example 1, part C-H, was used to prepare [1S-[R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](4-methoxyphenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide;

Example 6F

a) From the reaction of 1.00g (3.36mmol) of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane and 9.2g (67mmol) of 4-methoxybenzyl amine, one obtains 1.12g (76%) of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-ph nylbutyl]N-[(4-meth xyphenylmethyl)]amine, MH^+ 435. This amine (1.12g, 2.58mmol) was then reacted with tert-butylisocyanate (260mg, 2.58mmol) t

afford 1.35g (98%) of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenyl]-1-[(4-methoxyphenylmethyl)]amino-1-(1,1-dimethylethyl)amino]carbonyl]butane; MH^+ 534.

b) The CBZ protected compound (1.35g, 2.53mmol) was then deprotected by hydrogenation over 10% palladium-on-carbon and the resulting free amine coupled with N-CBZ-L-asparagine (684mg, 2.57mmol) in the presence of N-hydroxybenzotriazole (590mg, 3.85mmol) and EDC (543mg, 2.83mmol) to yield 442mg (29%) of [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](4-methoxyphenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[phenylmethylcarbamoyl)amino]-butanediamide; mp 175C (dec) and MH^+ 648. This compound (345mg, 0.53mmol) was then deprotected by hydrogenation over 10% palladium-on-carbon and the resulting free amine coupled with 2-quinolinecarboxylic acid N-hydroxy-succinimide ester (118mg, 0.44mmol), in the presence of N-methylmorpholine, to afford 108mg (31%) of pure [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](4-methoxyphenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide; mp 220C (dec) and MLi^+ 675.

Example 7

The procedure described in Example 1, part C-H, was used to prepare [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](n-butyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide.

a) From the reaction of 1.48g (5.0mmol) of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane and 7.314g (100.0mm l) f n-butyl amine, one obtains 1.50g (80%) of [2(R), 3(S)]-N-[[3-(phenylm thylcarbam yl)amin]-2-hydroxy-4-

phenylbutyl]N-[n-butyl)]amine. This amine (1.48g, 4.0mmol) was then reacted with tert-butylisocyanate (396mg, 4.0mmol) to afford 1.87g (100%) of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenyl]-1-[(n-butyl)]amino-1-(1,1-dimethylethyl)amino]carbonyl] butane as an oil.

b) The CBZ protected compound (1.87g, 4.0mmol) was then deprotected by hydrogenation over 10% palladium-on-carbon and the resulting free amine coupled with N-CBZ-L-asparagine (1.05g, 3.96mmol) in the presence of N-hydroxybenzotriazole (535mg, 7.9mmol) and EDC (759mg, 3.96mmol) to yield 1.75g (76%) of [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](n-butyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(phenylmethylcarbamoyl)amino]-butanediamide; mp 166-167C and MH^+ 584.

A solution of[1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl]n-butyl)amino]-2-hydroxy-1-(phenylmethy)propyl]-2-[(phenylmethylcarbamoyl)amino]-butanediamide (1.03g, 1.77 mmol) in 40 mL of abs. ethanol ws then deprotected by hydrogenolysis in the presence of 10% palladium on carbon catalyst to give, after filtration and concentration, the free amine (428mg) which was coupled with N-hydroxysuccinimide ester of 2-quinoline carboxylate (270mg, 1.0 mmol) in dichloromethane for 16 h to give 380 mg, 63% of [1S-[1R*(R*), 2S*]]-N^1[3-[[[1,1-dimethylethyl)amino]carbonyl](n-butyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide, mp 102.1-103°C.

Example 8

The procedure described in Example 1, part C-H, was used to prepare [1S-[1R*(R*), 2S]]- N^1[3-[[[(1,1-dimethylethyl)amino]carb nyl](phenylm thyl)amino]-2-

hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino]-butanediamide.

a) From the reaction of 1.48g (5.0mmol) of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane and 10.68g (100.0mmol) of benzyl amine, one obtains 1.88g (95%) of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenylbutyl]N-[(phenylmethyl)]amine. This amine (1.88g, 4.65mmol) was then reacted with tert-butylisocyanate (460.0mg, 4.6mmol) to afford 2.24g (96%) of [2(R), 3(S)]-N-[[3-(phenylmethylcarbamoyl)amino]-2-hydroxy-4-phenyl]-1-[(phenylmethyl)]amino-1-(1,1-dimethylethyl)amino]carbonyl] butane.

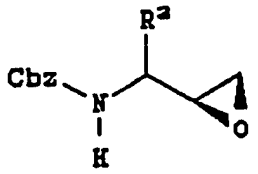
b) The CBZ protected compound (2.22g, 4.4mmol) was then deprotected by hydrogenation over 10% palladium-on-carbon and the resulting free amine coupled with N-CBZ-L-asparagine (1.17g, 4.4mmol) in the presence of N-hydroxybenzotriazole (1.19g, 8.8mmol) and EDC (843mg, 4.4mmol) to yield 2.11g (78%) of [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](phenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(phenylmethylcarbamoyl)amino]-butanediamide; mp 156-158C and MH^+ 618. This compound (1.0g, 1.62mmol) was then deprotected by hydrogenation over 10% palladium-on-carbon and the resulting free amine coupled with 2-quinolinecarboxylic acid N-hydroxysuccinimide ester (437mg, 1.62mmol), in the presence of N-methylmorpholine, to afford 640mg (62%) of pure [1S-[1R*(R*), 2S*]]- N^1[3-[[[(1,1-dimethylethyl)amino]carbonyl](phenylmethyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarb nyl)amino]-butanediamide; mp 110.5-112.5C and MH^+ 639.

EXAMPLE 9

Additional exemplary compounds of the present invention ar listed in Table 1. Thes compounds were prepared according to the following general procedures.

General Procedure for the Synthesis of 1,3-Diamino 4-phenyl Butan-2-ol Derivatives.

A mixture of the amine R^3NH_2 (20 equiv.) in dry isopropyl alcohol (20mL/mmol of epoxide to be converted) was heated to reflux and then treated with an N-Cbz amino epoxide of the formula:



from a solids addition funnel over a 10-15 minute period. After the addition is complete the solution was maintained at reflux for an additional 15 minutes and the progress of the reaction monitored by TLC. In nearly all cases the reaction was found to be complete after this time period. The reaction mixture was then concentrated in vacuo to give an oil that was treated with n-hexane with rapid stirring whereupon the ring opened material precipitated from solution. Precipitation was generally complete within 1 hr and the product was then isolated by filtration on a Büchner funnel and then air dried. The product was further dried in vacuo. This method affords amino alcohols of sufficient purity for most purposes.

General procedure for the Reaction of Amino Alcohols with Isocyanates: Preparation of Ureas

A solution from the amino alcohol in tetrahydrofuran (THF) was treated at room temperature with th appropriate is cyanate f formula R^4NCO via syringe under nitrogen. Aft r the reacti n has stirred f r ~5m the pr gress of the reacti n was m nitored by TLC. In nearly all cases the reacti n was complete.

The solvent was removed in vacuo and the product obtained was of sufficient purity for most purposes. The product may be further purified by dissolution in ethyl acetate and washing with 5% aqueous citric acid, water, and brine. The solvent is dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give the pure urea.

General Procedure for the Removal of the Protecting Groups by Hydrogenolysis with Palladium on Carbon

A. Alcohol Solvent

The Cbz-protected peptide derivative was dissolved in methanol (ca.20mL/mmol) and 10% palladium on carbon catalyst is added under a nitrogen atmosphere. The reaction vessel is sealed and flushed 5 times with nitrogen and then 5 times with hydrogen. The pressure is maintained at 50 psig for 1-16 hours and then the hydrogen replaced with nitrogen and the solution filtered through a pad of celite to remove the catalyst. The solvent is removed in vacuo to give the free amino derivative of suitable purity to be taken directly on to the next step.

B. Acetic Acid Solvent

The Cbz-protected peptide derivative was dissolved in glacial acetic acid (20mL/mmol) and 10% palladium on carbon catalyst is added under a nitrogen atmosphere. The reaction vessel is flushed 5 times with nitrogen and 5 times with hydrogen and then maintained at 40 psig for about 2h. The hydrogen was then replaced with nitrogen and the reaction mixture filtered through a pad of celite to remove the catalyst. The filtrate was concentrated and the resulting product taken up in anhydrous ether and evaporated to dryness 3 times. The final product, the acetate salt, was dried in vacuo and is f suitable purity for subsequent conversion.

General Procedure for Removal of Boc-protecting Group with 4N Hydrochloric Acid in Dioxane

The Boc-protected amino acid or peptide is treated with a solution of 4N HCl in dioxane with stirring at room temperature. Generally the deprotection reaction is complete within 15 minutes, the progress of the reaction is monitored by thin layer chromatography (TLC). Upon completion, the excess dioxane and HCl are removed by evaporation in vacuo. The last traces of dioxane and HCl are best removed by evaporation again from anhydrous ether or acetone. The hydrochloride salt thus obtained is thoroughly dried in vacuo and is suitable for further reaction.

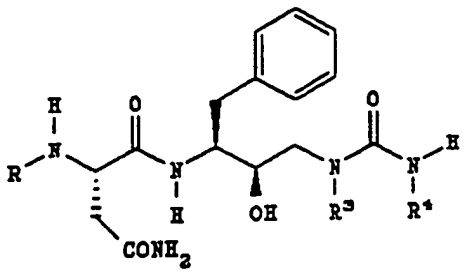
EDC/HOBt Coupling of Cbz-Asparagine (General Procedure)

N-CBZ-(L-asparagine (1.10eq) and N-hydroxybenzotriazole (HOBt) (1.5eq) are dissolved in dry dimethylformamide (DMF) (2-5mL/mmol) and cooled in an ice bath. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (1.10eq) is added to the stirring solution and maintained at 0°C for 10 minutes. A solution of the amino component (free amine), 1.0eq in DMF (1-2mL/mmol), is added. [In the case of the amine hydrochloride or acetate salt, an equivalent of N-methylmorpholine is also added.] The reaction mixture is stirred at 0°C for 1 hour and then at room temperature for ~5-6 hours. The reaction mixture is then poured into a rapidly stirring solution of 60% saturated aqueous sodium bicarbonate (ca-50mL/mmol). An immediate white precipitate forms which is collected on a Büchner funnel and the solid washed thoroughly with saturated aqueous sodium bicarbonate, water, 5% aqueous citric acid solution and water. The product is thoroughly dried in vacuo and redissolved in DMF, filtered and reprecipitated by the addition to water. The precipitated product is is lated by filtrati n, washed again with water and dried in vacuo.

General Procedure for Acylation with 2-Quinoline Carboxylic Acid N-Hydroxysuccinimide Ester

A solution of the free amin (or amine acetate salt) and 1.0 equivalent of N-hydroxysuccinimide 2-quinoline carboxylate in anhydrous dichloromethane was treated with 1.5 equivalents of N-methylmorpholine (NMM) at room temperature. The progress of the reaction was monitored by TLC and when the reaction was complete the reaction mixture was diluted with additional dichloromethane and the solution washed with saturated aqueous sodium bicarbonate, 5% aqueous citric acid, water and brine. The solution was dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo. The product thus obtained was recrystallized from a mixture of acetone and hexane.

TABLE 1



Entry No.	R	R^3	R^4
1	Cbz[a]	CH_3	n-Butyl
2	Cbz	i-Butyl	CH_3
3	Cbz	i-Butyl	n-Butyl
4	Q[b]	i-Butyl	n-Butyl
5	Cbz	i-Propyl	n-Butyl
6	Q	i-Propyl	n-Butyl
7	Cbz	C_6H_5	n-Butyl
8	Cbz	$-CH_2-C_6H_5$	n-Butyl
9	Cbz	$-CH_2-C_6H_5$	n-Butyl
10	Q	$-CH_2-C_6H_5$	n-Butyl
11	Cbz	$-C_6H_5$	n-Butyl
12	Cbz	i-Butyl	n-Propyl
13	Cbz	i-Butyl	$-CH_2CH(CH_3)_2$
14	Cbz	(R)-$CH(CH_3)-C_6H_5$	n-Butyl
15	Cbz	$-CH_2-C_6H_5$	i-Propyl
16	Cbz	$-CH_2-C_6H_5$	$-CH_2CH_2CH(CH_3)_2$
17	Cbz	i-Butyl	$-CH_2CH_3$
18	Cbz	i-Butyl	$-CH(CH_3)_2$

TABLE 1 (Cont'd)

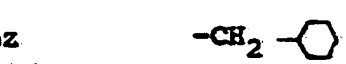
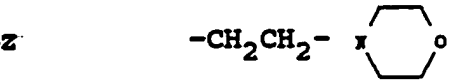
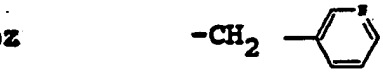
Entry No.	R	R^3	R^4
19	Cbz	i-Butyl	
20	Q	i-Butyl	
21	Cbz		$-(CH_2)_2CH(CH_3)_2$
22	Cbz	$(CH_2)_2CH(CH_3)_2$	$-CH(CH_3)_2$
23	Q	i-Butyl	$-CH(CH_3)_2$
24	Cbz	i-Butyl	$-C(CH_3)_3$
25	Q	i-Butyl	$-C(CH_3)_3$
26	Cbz		$-C(CH_3)_3$
27	Q		$-C(CH_3)_3$
28	Cbz	$-(CH_2)_2CH(CH_3)_2$	$-C(CH_3)_3$
29	Q	$-(CH_2)_2CH(CH_3)_2$	$-C(CH_3)_3$
30	Cbz	$-CH_2C_6H_5$	$-C(CH_3)_3$
31	Q	$-CH_2C_6H_5$	$-C(CH_3)_3$
32	Cbz	$-(CH_2)_2C_6H_5$	$-C(CH_3)_3$
33	Cbz	$-(CH_2)_2C_6H_5$	$-C(CH_3)_3$
34	Cbz	n-Butyl	$-C(CH_3)_3$
35	Cbz	n-Pentyl	$-C(CH_3)_3$
36	Cbz	n-Hexyl	$-C(CH_3)_3$
37	Cbz		$-C(CH_3)_3$
38	Cbz	$-CH_2C(CH_3)_3$	$-C(CH_3)_3$
39	Q	$-CH_2C(CH_3)_3$	$-C(CH_3)_3$
40	Cbz		$-C(CH_3)_3$
41	Cbz	$-CH_2C_6H_5OCH_3$ (para)	$-C(CH_3)_3$
42	Cbz		$-C(CH_3)_3$
43	Cbz		$-C(CH_3)_3$
44	Cbz	$-(CH_2)_2C(CH_3)_3$	$-C(CH_3)_3$
45	Q	$-(CH_2)_2C(CH_3)_3$	$-C(CH_3)_3$
46	Cbz	$-(CH_2)_4OH$	$-C(CH_3)_3$

TABLE 1 (Cont'd)

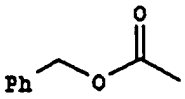
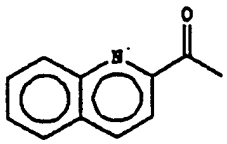
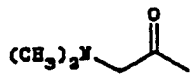
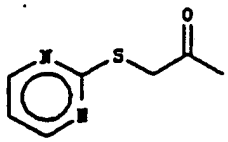
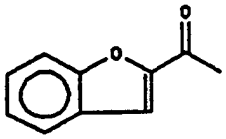
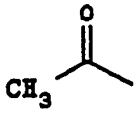
Entry No.	R	R^3	R^4
47.	Q	$-(CH_2)_4OH$	$-C(CH_3)_3$
48.	Q	$-CH_2-$  -F	$-C(CH_3)_3$
49.	Q	$-CH_2-$ 	$-C(CH_3)_3$
50.		$-(CH_2CH(CH_3)_2$	$-C(CH_3)_3$
51.		"	"
52.		"	"
53.		"	"
54.		"	"
55.		"	"

TABLE 1 (Cont'd)

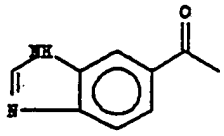
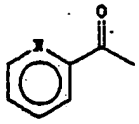
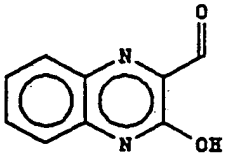
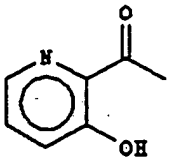
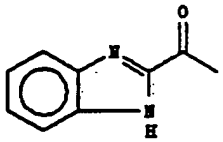
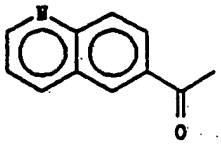
Entry No.	R	R^3	R^4
56.		"	"
57.		"	"
58.		"	"
59.		"	"
60.		"	"
61.		"	"

TABLE 1 (Cont'd)

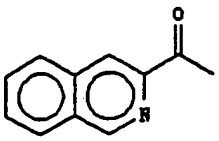
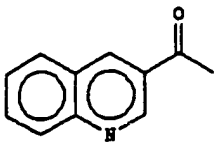
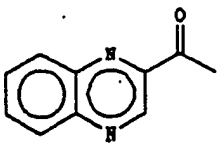
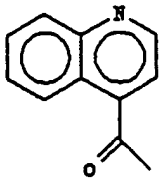
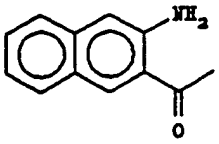
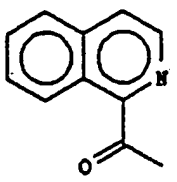
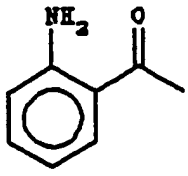
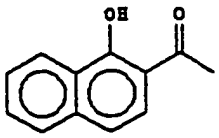
Entry No.	R	R^3	R^4
62.		"	"
63.		"	"
64.		"	"
65.		"	"
66.		"	"
67.		"	"
68.		"	"

TABLE 1 (Cont'd)

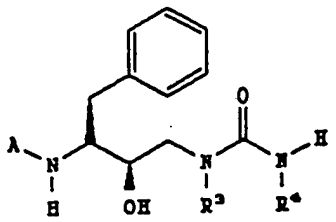
Entry No.	R	R^3	R^4
69.		"	"

[a] benzyloxycarbonyl
[b] 2-quinolinylcarbonyl

EXAMPLE 10

Following the generalized procedures set forth in Example 9, the compounds set forth in Table 2 were prepared.

TABLE 2



Entry	A	R^3	R^4
1.	Cbz-Val		i-amyl
tBu			
2.	Cbz-Leu	i-amyl	t-Bu
3.	Cbz-Ile	i-amyl	t-Bu
4.	Ac-D-homo-Phe	i-Bu	n-Bu
5.	Qui-Orn(γ-Cbz)	$-CH_2-$ ⬡	t-Bu
6.	Cbz-Asn	$-CH_2CH=CH_2$	t-Bu
7.	Acetyl-t-BuGly	i-amyl	t-Bu
8.	Acetyl-Phe	i-amyl	t-Bu
9.	Acetyl-Ile	i-amyl	t-Bu
10.	Acetyl-Leu	i-amyl	t-Bu
11.	Acetyl-His	i-amyl	t-Bu
12.	Acetyl-Thr	i-amyl	t-Bu
13.	Acetyl-NHCH($C(CH_3)_2(SCH_3)$)C(O)-	i-amyl	t-Bu
14.	Cbz-Asn	i-amyl	t-Bu
15.	Cbz-Ala	i-amyl	t-Bu
16.	Cbz-Ala	i-amyl	t-Bu
17.	Cbz-beta-cyanoAla	i-amyl	t-Bu
18.	Cbz-t-BuGly	i-amyl	t-Bu
19.	Q-t-BuGly	i-amyl	t-Bu
20.	Q-SCH_3Cys	i-amyl	t-Bu
21.	Cbz-SCH_3Cys	i-amyl	t-Bu

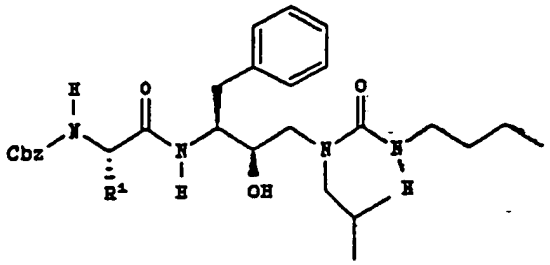
TABLE 2 (Cont'd)

Entry	A	R^3	R^4
22.	Q-Asp	i-amyl	t-Bu
23.	Cbz-(NHCH(C(CH_3)$_2$(SCH_3))C(O)-	i-amyl	t-Bu
24.	Cbz-EtGly	i-amyl	t-Bu
25.	Cbz-PrGly	i-amyl	t-Bu
26.	Cbz-Thr	i-amyl	t-Bu
27.	Q-Phe	i-amyl	t-Bu
28.	Cbz-Phe	i-amyl	t-Bu

EXAMPLE 11

Following the generalized procedure of Example 9, the compounds listed in Table 3 were prepared.

TABLE 3

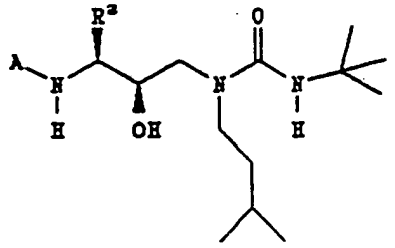


Entry	R^1
1	$CH_2SO_2CH_3$
2	(R)-CH(OH)CH_3
3	$CH(CH_3)_2$
4	(R,S)CH_2SOCH_3
5	$CH_2SO_2NH_2$
6	CH_2SCH_3
7	$CH_2CH(CH_3)_2$
8	$CH_2CH_2C(O)NH_2$
9	(S)-CH(OH)CH_3

EXAMPLE 12

Following the g neralized procedures of Example 6, Part D and Example 9, the compounds s t forth in Table 4 were prepared.

TABLE 4



Entry	R^2	A
1.	n-Bu	Cbz-Asn
2.	cyclohexylmethyl	Cbz-Asn
3.	n-Bu	Boc
4.	n-Bu	Cbz
5.	$C_6H_5CH_2$	Boc
6.	$C_6H_5CH_2$	Cbz
7.	$C_6H_5CH_2$	benzoyl
8.	cyclohexylmethyl	Cbz
9.	n-Bu	Q-Asn
10.	cyclohexylmethyl	Q-Asn
11.	$C_6H_5CH_2$	Cbz-Ile
12.	$C_6H_5CH_2$	Q-Ile
13.	$C_6H_5CH_2$	Cbz-t-BuGly
14.	$C_6H_5CH_2$	Q-t-BuGly
15.	$C_6H_5CH_2$	Cbz-Val
16.	$C_6H_5CH_2$	Q-Val
17.	2-naphthylmethyl	Cbz-Asn
18.	2-naphthylmethyl	Q-Asn
19.	2-naphthylmethyl	Cbz
20.	n-Bu	Cbz-Val

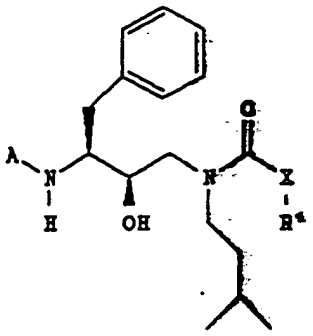
TABLE 4 (Cont'd)

Entry	R^2	A
21.	n-Bu	Q-Val
22.	n-Bu	Q-Ile
23.	n-Bu	Cbz-t-BuGly
24.	n-Bu	Q-t-BuGly
25.	p-F(C_6H_4)CH_2	Q-Asn
26.	p-F(C_6H_4)CH_2	Cbz
27.	p-F(C_6H_4)CH_2	Cbz-Asn

EXAMPLE 13

The compounds listed in Table 5 were prepared according to the generalized procedures of Example 9.

TABLE 5

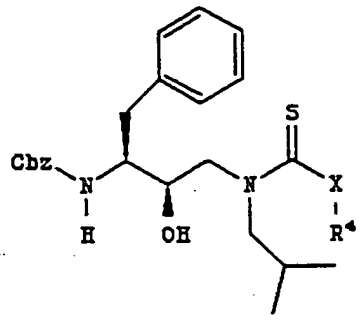


Entry	XR^4	A
1.	-NH^tBu	Cbz-Asn
2.	-NEt_2	Cbz
3.	-$NHC(CH_3)_2CH_2CH_3$	Cbz

EXAMPLE 14

The compounds of Table 6 were prepared according to the generalized procedures set forth in Example 9 except that instead of an isocyanate, an isothiocyanate equivalent was utilized.

Table 6



Entry	XHR^4
1.	NHEt
2.	NH^tBu

The Cbz group of the compounds shown in Examples 13 and 14 can be removed as described in Example 9 and the resulting compound can be coupled to a desired α- or β-amino acid or the like to produce compounds of the present invention.

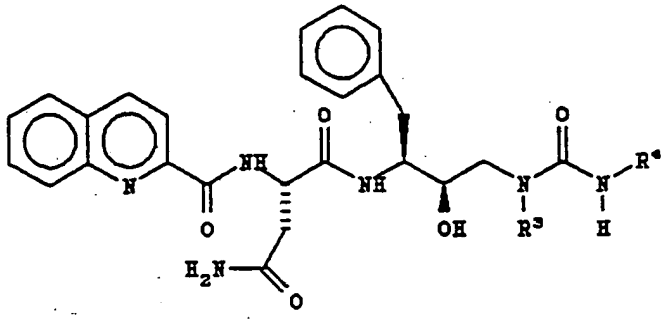
Example 15

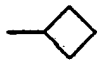
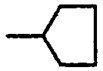
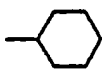
The compounds shown in Table 7 were prepared according to the following general procedure. This general procedure represents a Curtius Rearrangement and reaction with the amino alcohol derivative as prepared following the general procedure in Example 9.

To a solution of 1 mmol of carboxylic acid in 12 mL of toluene and 3 mmol of triethylamine at 90°C under a nitrogen atmosphere, was added 1 mmol of diphenylphosphoryl azide. After 1 hour, a solution of 1

mmol of amino alcohol derivative in 3.5 mL of either N,N-dimethylformamide or toluene was added. After 1 hour, the solvent was removed under reduced pressure, ethyl acetate and water added and the layers separated. The organic layer was washed with 5% citric acid, sodium bicarbonate, brine, dried, filtered and concentrated to afford the crude product. This was then recrystallized or chromatographed on silica gel to afford the purified final compound.

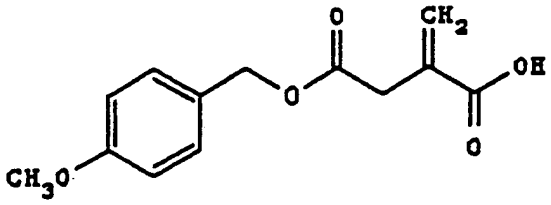
TABLE 7



R^3	R^4
$-CH_2CH(CH_3)_2$	$-C(CH_3)_2$
$-CH_2CH_2CH(CH_3)_2$	
$-CH_2CH_2CH(CH_3)_2$	
$-CH_2CH_2CH(CH_3)_2$	
$-CH_2CH_2CH(CH_3)_2$	

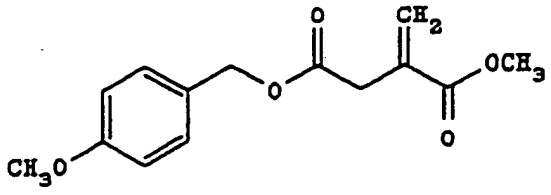
Example 16

A. Preparation of 4(4-methoxybenzyl)itaconate



A 5 L three-necked round bottomed flask equipped with constant pressure addition funnel, reflux condenser, nitrogen inlet, and mechanical stirrer was charged with itaconic anhydride (660.8g, 5.88 mol) and toluene (2300 mL). The solution was warmed to reflux and treated with 4-methoxybenzyl alcohol (812.4g, 5.88 mol) dropwise over a 2.6h period. The solution was maintained at reflux for an additional 1.5h and then the contents were poured into three 2 L erlenmeyer flasks to crystallize. The solution was allowed to cool to room temperature whereupon the desired mono-ester crystallized. The product was isolated by filtration on a Buchner funnel and air dried to give 850.2g, 58% of material with mp 83-85°C, a second crop, 17% was isolated after cooling of the filtrate in an ice bath. ^{1}H NMR ($CDCl_3$) 300 MHz 7.32(d, J=8.7 Hz, 2H), 6.91(d, J=8.7 Hz, 2H), 6.49(s, 1H), 5.85(s, 1H), 5.12(s, 2H), 3.83(s, 3H), 3.40(s, 2H).

B. Preparation of Methyl 4(4-methoxybenzyl) itaconate

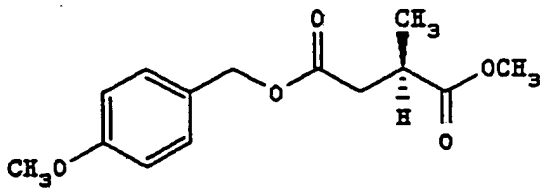


A 5 L three-necked round bottomed flask equipped with r flux condenser, nitrogen inlet, constant pressure additi n funnel and mechanical stirrer was charged with 4(4-methoxybenzyl) itaconate (453.4g, 1.81 mol) and treated with 1,5-diazabicyclo[4.3.0]non-5-ene (275.6g,

1.81 mol), (DBU), dropwise so that the temperature did not rise abov 15°C. To this stirring mixture was added a solution of methyl iodide (256.9g, 1.81 mol) in 250 mL of toluene from the dropping funnel over a 45m period. The solution was allowed to warm to room temperature and stirred for an additional 3.25h.

The precipitated DBU hydroiodide was removed by filtration, washed with toluene and the filtrate poured into a separatory funnel. The solution was washed with sat. aq. $NaHCO_3$ (2 X 500 mL), 0.2N HCl (1 X 500 mL), and brine (2 X 500 mL), dried over anhyd. $MgSO_4$, filtered, and the solvent removed in vacuo. This gave a clear colorless oil, 450.2g, 94% whose NMR was consistent with the assigned structure. ^1H NMR ($CDCl_3$) 300 MHz 7.30(d, J=8.7 Hz, 2H), 6.90(d, J=8.7 Hz, 2H), 6.34(s, 1H), 5.71(s, 1H), 5.09(s, 2H), 3.82(s, 3H), 3.73(s, 3H), 3.38(s, 2H). ^{13}C NMR (CDl_3) 170.46, 166.47, 159.51, 133.55, 129.97, 128.45, 127.72, 113.77, 66.36, 55.12, 51.94, 37.64.

C. Preparation of Methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate



A 500 mL Fisher-Porter bottle was charged with methyl 4(4-methoxybenzyl) itaconate (71.1g, 0.269 mol), rhodium (R,R) DiPAMP catalyst (204mg, 0.269 mmol, 0.1 mol%) and degassed methanol (215 mL). The bottle was flushed 5 times with nitrogen and 5 times with hydrogen to a final pressure of 40 psig. The hydrogenation commenced immediately and after ca. 1h the uptake began to taper off, after 3h the hydrog n uptak ceased and the bottle was flushed with nitrogen, opened and the contents c ncentrated n a rotary vaporator to give a brown oil

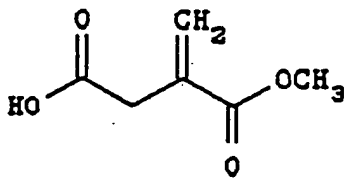
that was taken up in boiling iso-octane (ca. 200 mL, this was r peated twice), filtered through a pad of celite and the filtrate concentrated in vacuo to give 66.6g, 93% of a clear colorless oil, ^{1}H NMR ($CDCl_3$ 300 MHz 7.30(d, J=8.7 Hz, 2H), 6.91(d, J=8.7 Hz, 2H), 5.08(s, 2H), 3.82(s, 3H), 3.67(s, 3H), 2.95(ddq, J=5.7, 7.5, 8.7 Hz, 1H), 2.79(dd, J=8.1, 16.5 Hz, 1H), 2.45(dd, J=5.7, 16.5 Hz, 1H), 1.23(d, J=7.5 Hz, 3H).

D. Preparation of Methyl 2(R)-methylsuccinate

A 3 L three-necked round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer, reflux condenser and constant pressure addition funnel was charged with methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate (432.6g, 1.65 mol) and toluene (1200 mL). The stirrer was started and the solution treated with trifluoroacetic acid (600 mL) from the dropping funnel over 0.25h. The solution turned a deep purple color and the internal temperature rose to 45°C. After stirring for 2.25h the temperature was 27°C and the solution had acquired a pink color. The solution was concentrated on a rotary evaporator. The residue was diluted with water (2200 mL) and sat. aq. $NaHCO_3$ (1000 mL). Additional $NaHCO_3$ was added until the acid had been neutralized. The aqueous phase was extracted with ethyl acetate (2 X 1000 mL) to remove the by-products and the aqueous layer was acidified to pH=1.8 with conc. HCl. This solution was extracted with ethyl acetate (4 X 1000 mL), washed with brine, dried over anhyd. $MgSO_4$, filtered and concentrated on a rotary evaporator to give a colorless liquid 251g, >100% that was vacuum distilled through a short path apparatus cut 1: bath temperature 120°C @ >1mm, bp 25-29°C; cut 2: bath temperature 140°C @ 0.5mm, bp 95-108°C, 151g, $[\alpha]_D$ @ 25°C=+1.38°C(c=15.475, MeOH), $[\alpha]_D$=+8.48°C (neat); cut 3: bath temperature 140°C, bp 108°C, 36g, $[\alpha]_D$ @ 25°C=+1.49°C(c=15.00, MeOH), $[\alpha]_D$=+8.98°C (neat). Cuts 2 and 3 were combined to give 189g, 78% of product, ^{1}H

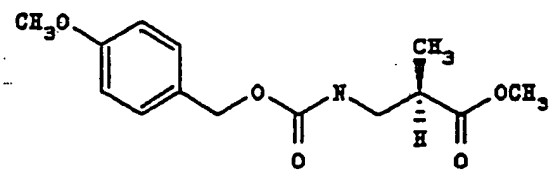
NMR ($CDCl_3$) 300 MHz 11.6(brs, 1H), 3.72(s, 3H), 2.92(ddq, J=5.7, 6.9, 8.0 Hz, 1H), 2.81(dd, J=8.0, 16.8 Hz, 1H), 2.47(dd, J=5.7, 16.8 Hz, 1H), 1.26(d, J=6.9 Hz, 3H).

E. Preparation of Methyl Itaconate



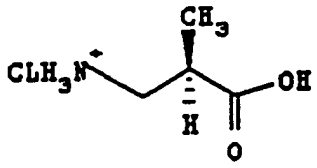
A 50 mL round bottomed flask equipped with reflux condenser, nitrogen inlet and magnetic stir bar was charged with methyl 4(4-methoxybenzyl) itaconate (4.00g, 16 mmol). The solution was kept at room temperature for 18 hours and then the volatiles were removed in vacuo. The residue was taken up in ethyl acetate and extracted three times with saturated aqueous sodium bicarbonate solution. The combined aqueous extract was acidified to pH=1 with aqueous potassium bisulfate and then extracted three times with ethyl acetate. The combined ethyl acetate solution was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The residue was then vacuum distilled to give 1.23g, 75% of pure product, bp 85-87 @ 0.1 mm. ^1H NMR ($CDCl_3$) 300 MHz 6.34(s, 1H), 5.73(s, 2H), 3.76(s, 3H), 3.38(s, 2H). ^{13}C NMR ($CDCl_3$) 177.03, 166.65, 129.220, 132.99, 52.27, 37.46.

F. Curtius Rearrangement of Methyl 2(R)-methylsuccinate: Preparation of Methyl N-Moz-α-methyl β-alanine.



A 5L four"necked round bottomed flask equipped with a nitrogen inlet, reflux condenser, mechanical stirrer, constant pressure addition funnel, and thermometer adapter was charged with methyl 2(R)-methylsuccinate (184.1g, 1.26 mol), triethylamine (165.6g, 218 mL, 1.64 mol, 1.3 equivalents), and toluene (1063 mL). The solution was warmed to 85°C and then treated dropwise with a solution of diphenylphosphoryl azide (346.8g, 1.26 mol) over a period of 1.2h. The solution was maintained at that temperature for an additional 1.0h and then the mixture was treated with 4-methoxybenzyl alcohol (174.1g, 1.26 mol) over a 0.33h period from the dropping funnel. The solution was stirred at 88°C for an additional 2.25h and then cooled to room temperature. The contents of the flask were poured into a separatory funnel and washed with sat. aq. $NaHCO_3$ (2 X 500 mL), 0.2N HCl (2 X 500 mL), brine (1 X 500 mL), dried over anhyd. $MgSO_4$, filtered, and concentrated in vacuo to give 302.3g, 85% of the desired product as a slightly brown oil. ^1H NMR ($CDCl_3$) 300 MHz 7.32(d, J=8.4 Hz, 2H), 6.91(d, J=8.4 Hz, 2H), 5.2(brm, 1H), 5.05(s, 2H), 3.83(s, 3H), 3.70(s, 3H), 3.35(m, 2H), 2.70(m, 2H), 1.20(d, J=7.2 Hz, 3H).

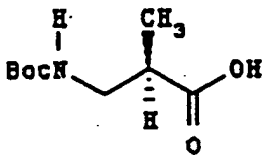
G. Hydrolysis of Methyl N-Moz-α-methyl β-alanine: Preparation of α-methyl β-alanine Hydrochloride



A 5 L three-necked round bottomed flask equipped with a reflux condenser, nitrogen inlet and mechanical stirrer was charged with methyl N-Moz-α-methyl β-alanine (218.6g, 0.78 mol), glacial acetic acid (975 mL) and 12N hydrochloric acid (1960 mL). The solution was then heated to reflux for 3h. After the

solution had co led to room temperature (ca. 1h) the aqueous phase was decanted from organic residue (polymer) and the aqueous phas conc ntrated on a rotary evaporator. Upon addition of acetone to the concentrated residue a slightly yellow solid formed that was slurried with acetone and the white solid was isolated by filtration on a Buchner funnel. The last traces of acetone were removed by evacuation to give 97.7g, 90% of pure product, mp 128.5-130.5°C $[\alpha]_D$ @ 25°C=9.0°C (c=2.535, Methanol). ^1H NMR (D_2O) 300 MHz 3.29(dd, J=8.6, 13.0 Hz, 1H), 3.16(dd, J=5.0, 13.0m Hz, 1H), 2.94(ddq, J=7.2, 5.0, 8.6 Hz, 1H), 1.30(d,J=7.2 Hz, 3H); ^{13}C NMR (D_2O) 180.84, 44.56, 40.27, 17.49.

H. Preparation of N-Boc α-Methyl β-Alanine



A solution of α-methyl β-alanine hydrochloride (97.7g, 0.70 mol) in water (1050 mL) and dioxane (1050 mL) the pH was adjusted to 8.9 with 2.9N NaOH solution. This stirring solution was then treated with di-tert-butyl pyrocarbonate (183.3g, 0.84 mol, 1.2 equivalents) all at once. The pH of the solution was maintained between 8.7 and 9.0 by the periodic addition of 2.5N NaOH solution. After 2.5h the pH had stabilized and the reaction was judged to be complete. The solution was concentrated on a rotary evaporator (the temperature was maintained at <40°C). The excess di-tert-butyl pyrocarbonate was removed by extraction with dichloromethane and then the aqueous solution was acidified with cold 1N HCl and immediately extracted with ethyl acetate (4 X 1000 mL). The combined ethyl acetate extract was wash d with brine, dried over anhyd. $MgSO_4$, filter d and c ncentrated on a rotary evap rator to give a thick il 127.3g, 90% crude yield that was stirred with n-hexane whereupon crystals f pure pr duct

formed, 95.65g, 67%, mp 76-78°C, $[\alpha]_D$ @ 25°C=-11.8°C (c=2.4, EtOH). A second crop was obtain d by concentration of the filtrate and dilution with hexane, 15.4g, for a combined yield of 111.05g, 78%. ^1H NMR (acetone D_6) 300 MHz 11.7 (brs, 1H), 6.05 (brs 1H), 3.35 (m, 1H), 3.22 (m, 1H), 2.50 (m, 1H), 1.45(s, 9H), 1.19 (d, J=7.3 Hz, 3H); ^{13}C NMR (acetone D_6) 177.01, 79.28, 44.44, 40.92, 29.08, 15.50. Elemental analysis calc'd. for $C_9H_{17}NO_4$: C, 53.19, H, 8.42; N, 6.89. Found: C, 53.36; H, 8.46; N, 6.99.

I. Preparation of N-4-Methoxybenzyloxycarbonyl α-Methyl β-Alanine

A solution of N-4-methoxybenzyloxycarbonyl α-methyl β-alanine methyl ester (2.81g, 10.0 mmol) in 30 mL of 25% aqueous methanol was treated with lithium hydroxide (1.3 equivalents) at room temperature for a period of 2h. The solution was concentrated in vacuo and the residue taken up in a mixture of water and ether and the phases separated and the organic phase discarded. The aqueous phase was acidified with aqueous potassium hydrogen sulfate to pH=1.5 and then extracted three times with ether. The combined ethereal phase was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 2.60 g, 97% of N-4-Methoxybenzyloxycarbonyl α-methyl β-alanine (N-Moz-AMBA) which was purified by recrystallization from a mixture of ethyl acetate and hexane to give 2.44g, 91% of pure product, mp 96-97°C, MH+=268. ^1H NMR (D_6-acetone/300 MHz) 1.16 (3H, d, J=7.2Hz), 2.70 (1H, m), 3.31 (2H, m), 3.31 (3H, s), 4.99 (2H, s), 6.92 (2H, 4, J=8.7 Hz), 7.13 (2H, d, J=8.7 Hz).

J. Preparation of Propanamide, 3-(4-methoxybenzyloxycarbonyl)-N_[3-[[[(1,1-dimethylethyl)amine]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl-[IS-[IR*(S*), 2S*]]-

N-Moz-AMBA (468mg, 1.75mmol) was dissolved in 5mL of DMF, HOBT (355mg, 2.6mmol) was added and the solution was cooled to 0°C. The solution was treated with (336mg, 1.75mmol) EDC for 15 minutes. To this was added (612mg, 1.75mmol) of [2R,3S 3-amino-1-isoamyl-1-(t-butylcarbonyl)amino 4-phenyl-2-butanol in 10mL of DMF and the reaction stirred for 16 hours at room temperature. The DMF was concentrated to 5mL and the product was precipitated by addition to 60% saturated aqueous $NaHCO_3$. The solid was taken up in ethyl acetate and washed with $KHSO_4$, $NaHCO_3$, NaCl(saturated), dried over $MgSO_4$ and concentrated to yield 680mg of crude product which was crystallized from CH_2Cl_2, Et_2O, hexane, to yield 300mg of pure product.

Example 17

The compounds of Table 8 were prepared according to the procedure listed below and that utilized in Example 16.

Propaneamide, 3-[(1,1-dimethylethyl)butoxycarbonyl]amino-N-[3-[[[(1,1--dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl-,[1S-[1R*(S*),2S*]-

Part A.

A solution of N-t-butyloxycarbonyl-2-(R)-methyl-3-aminopropionic acid (372 mg, 1.83 mmol) and N-hydroxybenzotriazole (371 mg, 2.75 mmol) in 5 mL of dimethylformamide was cooled to 0 degrees C. To this was added EDC (351 mg, 1.83 mmol) and the solution was stirr d for 15 minutes. To this chilled solution was added a solution of 3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyrl)amino]-2(R)-hydroxy-1(S)(phenylmethyl)pr pylamine in 5 mL of

dimethylformamide and stirr d for 15 hours. The dimethylformamide was r moved and replaced with 50 mL of ethyl acetate, and the organic phase was extracted with 5% potassium hydrogen sulfate, saturated sodium bicarbonate and brine. The ethyl acetate layer was dried over magnesium sulfate, filtered and concentrated to yield 613 mg of product after recrystallization from ethyl acetate , hexanes. (63 % yield). M+Li 541

Part B.

Preparation of Propaneamide,_3-amino-N-[3-[[[(1,1-dimethylethyl)amino] carbonyl]- (3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl-,[1S-[1R*(S*), 2S*]-hydrochloride

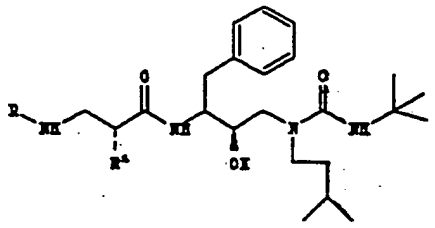
The product from part A. (577 mg, 1.08 mmol) was dissolved in 40 mL of 4N HCl in dioxane and the solution stirred for 2 hours, and concentrated to yield the hydrochloride salt in quantitative yield.

Part C.

Preparation of Propaneamide, 3-(2-methylpropanoylamino)-N-[3-[[[(1,1-dimethylethyl)-amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl-,[1S-[1R*(S*),2S*]-

The product from part B. (236 mg, 0.5 mmol) was dissolved in anhydrous tetrahydrofuran and to this was added N-methylmorpholine (160 mg, 1.5 mmol) upon which time a precipitate formed. To this suspension was added isobutyryl chloride (53.5 mg, 0.5 mmol) and the suspension stirred for 15 hours. The suspension was diluted with ethyl acetate and washed with 5% potassium hydrogen sulfate, saturated sodium bicarbonate and brine. the organic layer was dried over magnesium sulfate, filtered and concentrated to yield 195 mg of crude product which was chromatographed on silica gel with 5% methan l m thylene chl ride t yield 121.5 mg (50 % yield) of pure pr duct. M+Li 511

TABLE 8



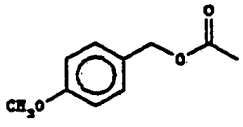
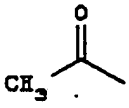
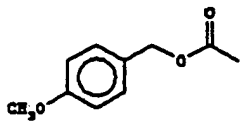
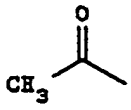
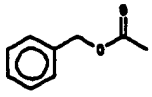
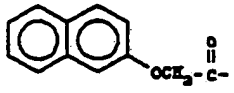
	R	R_1
1.		$-CH_3$
2.		$-CH_3$
3.		$-CH(CH_3)_2$
4.		$-CH(CH_3)_2$
5.		$-C(CH_3)_3$
6.		$-CH_3$

TABLE 8 (Cont'd)

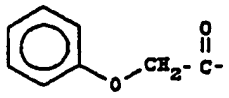
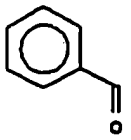
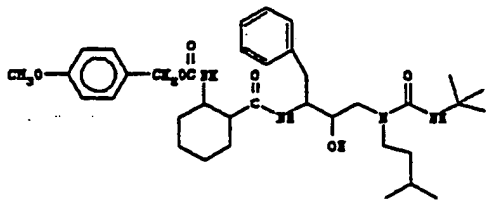
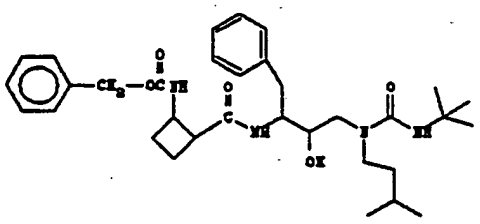
	R	R_1
7.		$-CH_3$
8.	$HO_2CCH_2CH_2-\overset{O}{\overset{\|}{C}}-$	"
9.		"
10.	$CH_3NH-\overset{O}{\overset{\|}{C}}-$	"
11.	$(CH_3)_2CH-\overset{O}{\overset{\|}{C}}-$	"
12.	$CH_3OCH_2-\overset{O}{\overset{\|}{C}}-$	"
13.	$(CH_3)_2NCH_2-\overset{O}{\overset{\|}{C}}-$	"
14.	$CH_3CH(OH)-\overset{O}{\overset{\|}{C}}-$	"

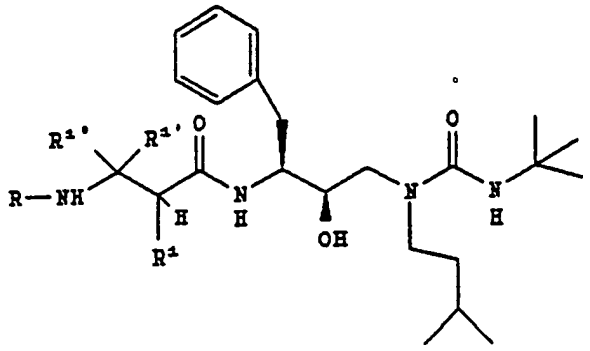
TABLE 8 (Cont'd)

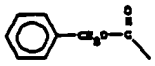
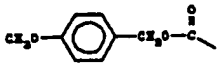
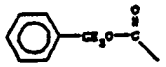
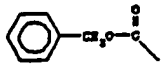
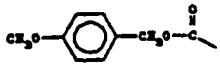
	R	R_1
15.		
16.		

Example 18

Following generally the procedure set forth in Example 16, the compounds shown in Table 9 were prepared.

TABLE 9

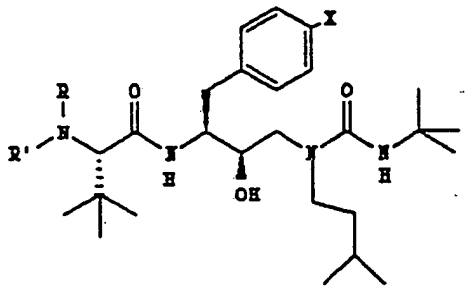


R^1	$R^{1'}$	$R^{1''}$	R
H	H	H	
H	H	H	
H	CH_3	H	
H	CH_3	CH_3	
H	H	CO_2CH_3	
H	H	H	
H	H	H	

Example 19

The procedure set forth below was generally utilized to prepare the compounds shown in Table 9

TABLE 10



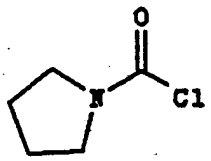
R	R'	X
R=H	R'=H	X=H
R=Me R'=Me	X=H	
R=H R'=Me		X=H
R=Me R'=Me	X=F	
R=H R'=Me		X=F
R=Cbz R'=Me		X=H
R=H R'=Bz		X=H
R+R'= pyrrole*		X=H

* Ile in place of t-butylglycine

Example 20

This example illustrates preparation of compounds wherein R^4 and R^5 together with N, forms a heterocycloalkyl radical.

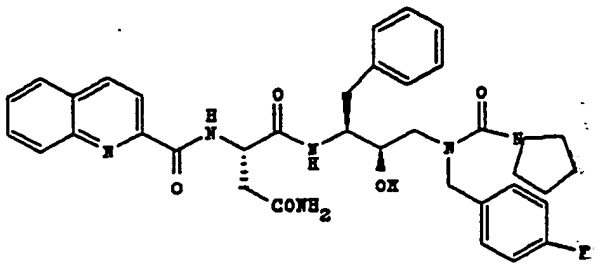
a) Pyrrolidine carbamoyl chloride.



A stirring solution of triphosgene (27.78g, 0.103 mol) in 40 mL toluene was cooled to -20 °C in an ice/salt bath under a blanket of nitrogen and treated with a solution of N-methylmorpholine (27.3 g, 0.27 mol) in 20

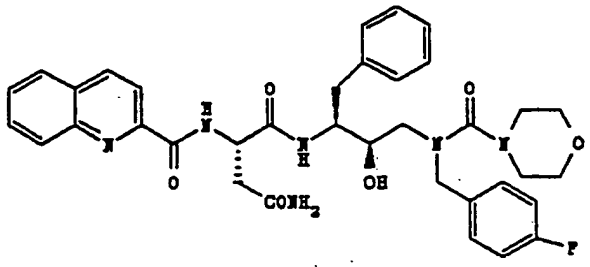
mL of toluen dropwise over 1h. This solution was then treated with a solution of pyrrolidin (19.8 g, 0.27 mol) in 30 mL of t luene over a peri d of 30 m. The solution was allowed to warm to room temperature, filtered and the filtrate concentrated in vacuo to give an oil that was purified by vacuum distillation through a 12" Vigeraux column to give 20.7g, 56%, bp 58 °C @ 0.6 mm, of pure product.

b) Butanediamide, N^1-[3-[[(4-fluorophenyl)methyl)](1-pyrrolidinylcarbonyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl) amino]-[1S[1R*(R*),2S*]]-



A stirring solution of [1S-[1R*(R*),2S*]]-N^1-[3-[[(4-fluorophenyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino-butanediamide (1.08 g, 1.91 mmol) in 7 mL of anhydrous DMF was treated with pyrrolidine carbamoyl chloride (260 mg, 1.95 mmol), 4-dimethylaminopyridine (15 mg), and N-methylmorpholine (380 mg, 3.76 mmol). The solution was stirred at room temperature for 3h and then concentrated in vacuo to give a semi-solid that was dissolved in methanol/water ca. 2:1. A solid formed from this solid that was isolated by filtration on a Büchner funnel and washed with water, 5% aq. citric acid and water and air dried to give 130 mg f pure pr duct, TLC n SiO_2 eluting with 7% m thanol in ethyl acetat showed one spot with R_f=0.64, 11%.

c) Butanediamide, N^1-[3-[[(4-fluorophenyl)methyl)](4-morph linylcarbonyl)amino]-2-hydroxy-1-(phenylmethyl)pr pyl]-2-[(2-quinolinylcarbonyl) amino]-[1S[1R*(R*),2S*]]-

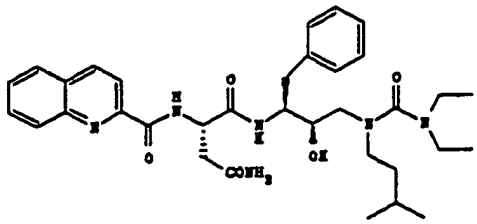


To a stirring solution of [1S-[1R*(R*),2S*]]-N^1-[3-[[(4-fluorophenyl)methyl]amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino-butanediamide (520 mg, 0.922 mmol), triethylamine (172 mg, 1.70 mmol), 4-dimethylaminopyridine (50 mg), and morpholino carbamoyl chloride (157.3 mg, 1.05 mmol) in 5 mL of chloroform. The initially heterogeneous mixture was heated to reflux for 6 h. The solution was then diluted with additional chloroform, poured into a separatory funnel and washed with 1N $KHSO_4$, sat. aq. $NaHCO_3$, dried over anhyd. $MgSO_4$, filtered, and concentrated <u>in vacuo</u> to give a white solid that was purified by column chromatography on SiO_2 eluting with ethanol/ethyl acetate to give 380 mg, 61%, of pure product.

Example 21

This example illustrates preparation of compounds wherein R^4 and R^5 are both other than H.

Butanediamide, N^1-[3-[[(diethylamino)carbonyl](3-methylbutyl)amino]-2- hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl) amino]-[1S-[1R*(R*),2S*]]-

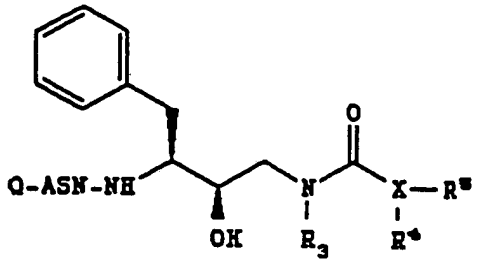


To a stirring solution of [1S-[1R*(R*),2S*]]-N^1-[3-(methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-[(2-quinolinylcarbonyl)amino-butane diamide] (119 mg, 0.21 mmol) triethylamine (59 mg, 0.58 mmol), 4-dimethylaminopyridine (9 mg), and diethyl carbamoyl chloride (157.3 mg, 1.05 mmol) in 4 mL of chloroform. The mixture was kept at room temperature for 26 h. The solution was then diluted with additional chloroform, poured into a separatory funnel and washed with 1N $KHSO_4$, sat. aq. $NaHCO_3$, dried over anhyd. $MgSO_4$, filtered, and concentrated in vacuo to give a white solid that was purified by column chromatography on SiO_2 eluting with methanol/CH_2Cl_2 to give 20 mg, 15%, of pure product.

Example 22

Following the procedures set forth in Example 26, the compounds listed in Table 11 were prepared.

TABLE 11



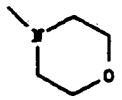
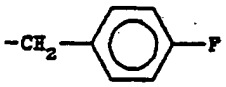
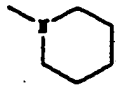
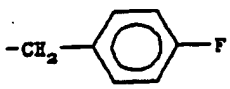
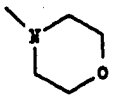
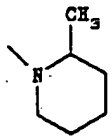
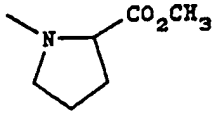
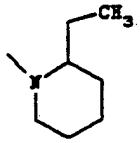
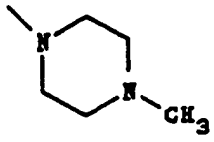
R_3	$X-R_4$ (with R^5)
$-CH_2CH(CH_3)_2$	$-N(CH_3)_2$
n	$-N(CH_2CH_3)_2$
n	$-N(CH(CH_3)_2)_2$
$-CH_2CH_2CH(CH_3)_2$	$-N(CH_3)_2$
n	$-N(CH_2CH_3)_2$
n	
	$-N(CH_3)_2$ $-N(CH_2CH_3)_2$
n	

TABLE 11 (Cont'd)

R_3	$X\text{-}R_4$ (with R^5)
	
"	$N(CH_3)(t\text{-}Bu)$
"	
"	
"	
"	

Example 23

3-[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino-2(R)-hydroxy-1(S)-(phenylmethyl)propyl amine

This example illustrates preparation of compounds of Formula II wherein R^1 is an alkyl group other than an alkyl group of a naturally occurring amino acid side chain.

Part A:

3-[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino-2(R)-hydroxy-1(S)-[N-(benzyloxycarbonyl)(phenylmethyl()propyl amine] (4.7 gm, 9.7 mmol) was combined with 10% Pd on carbon (200 mg) and conc. HCl (3 mL) in ethanol (35 mL) and hydrogenated at 50 psi of hydrogen for 2.5 h. The reaction mixture was filtered through diatomaceous earth and concentrated on a rotary evaporator to a yellow hygroscopic solid; 3.7 gm, 100%.

Part B:

Butaneamide, 2-[(phenylmethyloxycarbonyl)amino]-N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl-3,3-dimethyl-[1S-[1R*(R*),2S*]]-

N-Cbz-L-tert-leucine (172 mg, 0.65 mmol) and N-hydroxybenzotriazole (100 mg, 0.65 mmol) in DMF (3 mL) was cooled to 0 C and EDC (115 mg, 0.60 mmol) added. After 45 min the amine from Part A (193 mg, 0.50 mmol) and N-methylmorpholine (60 uL, 0.55 mmol) were added. The reaction was stirred at ambient temperature for 18 h and poured into a solution of 50% saturated $NaHCO_3$ (25 mL). The solid was collected by suction filtration, washed with water and dried in-vacuo. The solid was chromatographed on SiO_2 using 2% MeOH in CH_2Cl_2. The appropriate fractions were pooled and concentrated to afford a white solid; 220 mg, MH^+ 597, TLC (SiO_2 2%MeOH/CH_2Cl_2) R_f = .2. CHN requires: C, 68.42, H, 8.78, N, 9.39; found: C, 68.03, H, 8.83, N, 9.33.

Part C:

Butaneamide, 2-amino-N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl-3,3-dimethyl-, [1S-[1R*(R*), 2S*]-

The product from Part B (570 mg, 0.95 mmol) and 4% Pd on carbon (150 mg) in ethanol (30 mL) was hydrogenated at 5 psi for 2.75 h. The reaction mixture was filtered through diatomaceous earth and concentrated on a rotary evaporator to an oil; 438 mg, 100%.

Part D:

Butaneamide, 2-(acetylamino)-N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl-3,3-dimethyl-, [1S-[1R*(R*), 2S*]-

The product from Part C (206 mg, 0.41 mmol) and N-methylmorpholine (45 uL, 0.41 mmol) were dissolved in CH_2Cl_2 (2.5 mL) and cooled to 0 C. Acetic anhydride (39 uL, 0.41 mmol) was then added and the reaction stirred 30 min at 0 C, then allowed to warm to ambient temperature and stir for 30 min. The solvent was removed on a rotary evaporator and the residue dissolved in ethanol (2 mL). The ethanolic solution was slowly poured into 50 % saturated $NaHCO_3$ (20 mL) and stirred vigorously. The solid was collected by suction filtration and washed with water, 5% citric acid, and again with water; 157 mg, 75%. CHN / 1.5 H_2O requires: C 63.24, H, 9.67, N, 10.54; found:
C, 63.40, H, 9.41, N, 10.39.

Butaneamide, 2-amino-N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl-3,3-dimethyl-, [1S-[1R*(R*), 2S*]- was also capped with the acyl groups shown in Table 12.

TABLE 12

Acyl Group (R)
benzyloxycarbonyl
tert-butoxycarbonyl
acetyl
2-quinoylcarbonyl
phenoxyacetyl
benzoyl
methyloxaloyl
pivaloyl
trifluoracetyl
bromoacetyl
hydroxyacetyl
morpholinylacetyl
N,N-dimethylaminoacetyl
N-benzylaminoacetyl
N-phenylaminoacetyl
N-benzyl-N-methylaminoacetyl
N-methyl-N-(2-hydroxyethyl)aminoacetyl
N-methylcarbamoyl
3-methylbutyryl
N-isobutylcarbamoyl
succinoyl (3-carboxypropionyl)
carbamoyl

Example 24A

The procedure described below illustrates preparation of compounds of Formula III.

Propanamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl-3-(2-phenylethylsulfonyl)-,[1S-[1R*(R*),2S*]] and its diastereomer.

Part A

A solution of methyl methacrylate (7.25 g, 72.5 mmol) and phenethyl mercaptan (10.0 g, 72.5 mmol) in 100 mL of methanol was cooled in an ice bath and treated with sodium methoxide (100 mg, 1.85 mmol). The solution was stirred under nitrogen for 3 h and then concentrated *in vacuo* to give an oil that was taken up in ether and washed with 1 N aqueous potassium hydrogen sulfate, saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated to give 16.83 g, 97.5% of methyl 2-(R,S)-methyl-4-thia-6-phenyl hexanoate as an oil. TLC on SiO_2 eluting with 20:1 hexane:ethyl acetate (v:v) R_f=0.41.

Part B

A solution of methyl 2-(R,S)-methyl-4-thia-6-phenyl hexanoate (4.00 g, 16.8 mmol) in 100 mL of dichloromethane was stirred at room temperature and treated portion wise with meta-chloroperoxybenzoic acid (7.38 g, 39.2 mmol) over approximately 40 m. The solution was stirred at room temperature for 16 h and then filtered and the filterate washed with saturated aqueous sodium bicarbonate, 1N sodium hydroxide, saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 4.50 g, 99% of desired sulfone. The unpurified sulfone was dissolved in 100 mL of tetrahydrofuran and treated with a soluti n of lithium hydroxide (1.04 g, 24.5 mmol) in 40 mL of wat r. The s lution was stirred at r om temp rature for 2 m and then concentrated *in vacuo*. Th r sidue was then acidified with 1N aqueous potassium

hydrogen sulfate to pH=1 and then extracted three times with ethyl acetate. The combined ethyl acetate solution was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated to give a white solid. The solid was taken up in boiling ethyl acetate/hexane and allowed to stand undisturbed whereupon white needles formed that were isolated by filtration and air dried to give 3.38 g, 79% of 2-(R,S)-methyl-3(β-phenethylsulfonyl)-propionic acid, mp 91-93°C.

Part C

A solution of 2-(R,S)-methyl-3(β-phenethylsulfonyl)-propionic acid (166.1 mg, 0.65 mmol), N-hydroxybenzotriazole (HOBT) (146.9 mg, 0.97 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (145.8 mg, 0.75 mmol) in 4 mL of anhydrous dimethylformamide (DMF) cooled to 0°C and stirred under nitrogen for 0.5 h. This solution was then treated with 3-[[(dimethylethyl)amino]carbonyl](3-methylbutyl)amino-2(R)-hydroxy-1(S)-(phenylmethyl)propyl amine (201.9 mg, 0.59 mmol) and stirred at room temperature for 16 h. The solution was poured into 30 mL of 60% saturated aqueous sodium bicarbonate solution. The aqueous solution was then decanted from the organic residue. The organic residue was taken up in dichloromethane and washed with 10% aqueous citric acid, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give 110.0 mg, 32% of (2R,3S)-3-[N-2-(R)-methyl-3-(β-phenethylsulfonyl)propionyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol and (2R,3S)-3-[N-2-(S)-methyl-3-(β-phenethylsulfonyl)propionyl]amido-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol, FAB mass spectrum (MH+) =588. Flash chromatography of the mixture n silica gel eluting with 1:1 hexane:ethyl acetate afforded the separat d diastere mers.

Example 24B

Propanamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl-3-(methylsulfonyl)- [1S-[1R*(R*), 2S*]], and its diastereomer.

Part A

A solution of methyl 2-(bromomethyl)-acrylate (26.4 g, 0.148 mol) in 100 mL of methanol was treated with sodium methanesulfinate (15.1 g, 0.148 mol) portion wise over 10 m at room temperature. The solution was then stirred at room temperature for a period of 1.25 h and the solution concentrated *in vacuo*. The residue was then taken up in water and extracted four times with ethyl acetate. The combined ethyl acetate solution was washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered and concentrated to give a white solid, 20.7 g which was taken up in boiling acetone/methyl tert-butyl ether and allowed to stand whereupon crystals of pure methyl 2-(methylsulfonylmethyl) acrylate 18.0 g, 68% formed, mp 65-68 0°C.

Part B

A solution of methyl 2-(methylsulfonylmethyl) acrylate (970 mg, 5.44 mmol) in 15 mL of tetrahydrofuran was treated with a solution of lithium hydroxide (270 mg, 6.4 mmol) in 7 mL of water. The solution was stirred at room temperature for 5 m and then acidified to pH=1 with 1 N aqueous potassium hydrogen sulfate and the solution extracted three times with ethyl acetate. The combined ethyl acetate solution was dried over anhydrous magnesium sulfate, filtered, and concentrated to give 793 mg, 89% of 2-(methylsulfonylmethyl) acrylic acid, mp 147-149 0°C.

Part C

A solution f 2-(methylsulfonylmethyl) acrylic acid (700 mg, 4.26 mmol) in 20 mL f methan l was charged into a Fisher-Porter bottl along with 10%

palladium on carbon catalyst under a nitrogen atmosphere. The reaction vessel was sealed and flushed five times with nitrogen and then fiv times with hydrogen. The pressure was maintained at 50 psig for 16 h and then the hydrogen was replaced with nitrogen and the solution filtered through a pad of celite to remove the catalyst and the filterate concentrated *in vacuo* to give 682 mg 96% of 2-(R,S)-methyl-3-methylsulfonyl propionic acid.

Part D

A solution of 2-(R,S)-methyl-3(methylsulfonyl) propionic acid (263.5 mg, 1.585 mmol), N-hydroxybenzotriazole (HOBT) (322.2 mg, 2.13 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (339.1 mg, 1.74 mmol) in 4 mL of anhydrous dimethylformamide (DMF) cooled to 0°C and stirred under nitrogen for 0.5 h. This solution was then treated with 3-[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino-2(R)-hydroxy-I(S)-(phenylmethyl)propyl amine (543.5 mg, 1.58 mmol) and stirred at room temperature for 16 h. The solution was poured into 60 mL of 60% saturated aqueous sodium bicarbonate solution. The aqueous solution was then decanted from the organic residue. The organic residue was taken up in dichloromethane and washed with 10% aqueous citric acid, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to give 471.8 mg, 60% of Propanamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl-3-(methylsulfonyl)-, [1S-[1R*(R*), 2S*]]- and its diastereomer.

Example 25

Preparation of Sulfone Inhibitors From L-(+)-S-acetyl-β-mercaptoisobutyric Acid

Part A:

Propanamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amin]-2-

hydroxy-1-(phenylmethyl)propyl]-2-methyl-3-S-acetyl)-[1S-[1R*),2S*]]-.

A round-bottomed flask was charged with (2R,3R)-3-amino-1-isoamyl-1-(tert-butylcarbamoyl)amino-4-phenyl-2-butanol (901.5 mg, 2.575 mmol), L-(+)-S-acetyl-b-mercaptoisobutyric acid (164.5 mg, 2.575 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (339.1 mg, 1.74 mmol), and 10 mL of CH_2Cl_2 and allowed to stir at room temperature for 16 h. The solution was concentrated in vacuo and the residue taken up in ethyl acetate, washed with 1N $KHSO_4$ sat. aq. $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give an oil that was purified by radial chromatography on SiO_2 eluting with ethyl acetate to give the pure product, 800 mg, 63%.

Part B:

Propanamide, N-[3-[[[1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl-3-mercapto)-, [1S-[1R*(R*),2S*]]-.

A solution of [1S-[1R*(R*),2S*]]- N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl-3-S-acetyl)-propanamide (420 mg, 0.85 mmol) in 10 mL of methanol was treated with anhydrous ammonia for ca. 1 m at 0°C. The solution was stirred at that temperature for 16 h and then concentrated in vacuo to give 380 mg, 99%, of the desired product that was used directly in the next step without further purification.

Part C:

Propanamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl-3-S-methyl-, [1S-[1R*(R*),2S*]]-.

A solution f [1S-[1R*(R*),2S*]]- N-[3-[[[(1,1-dim thylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydr xy-1-(phenylmethyl)pr pyl]-2-methyl-3-mercapto)-pr panamide (380 mg, 0.841 mm l) in

10 mL of dry toluene under nitrogen was treated in rapid succession with 1,8-diazabicyclo[5.4.0]undec-7-en , (DBU), (128.1 mg. 0.841 mmol) and iodomethane (119.0 mg, 0.841 mmol). After 0.5 h at room temperature the reaction was found to be complete and the solution was diluted with ethyl acetate washed with 1N $KHSO_4$, sat. aq. $NaHCO_3$, brine. After the solution was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo the desired product was obtained as white foam was obtained, 370 mg, 94.5%, that was used directed in the next step.

Part D:

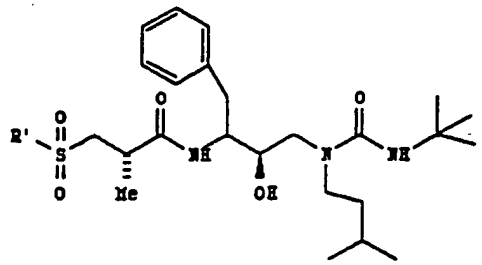
Propanamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl-3-(methylsulfonyl)-, [1S-[1R*(R*),2S*]]-.

A solution of [1S-[1R*(R*),2S*]]-N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl-3-S-methyl)-propanamide (340 mg, 0.73 mmol) and sodium perborate (500 mg, 3.25 mmol) in 30 mL of glacial acetic acid was warmed to 55°C for 16 h. The solution was concentrated in vacuo and then the residue taken up in ethyl acetate, washed with water, sat. aq. $NaHCO_3$, brine, dried over anhydrous $MgSO_4$, filtered and concentrated to give the desired product as a white solid, 350 mg, 96%.

Example 26

The compounds shown in Table 12 was prepared generally according to the procedure set forth in Examples 24 and 25.

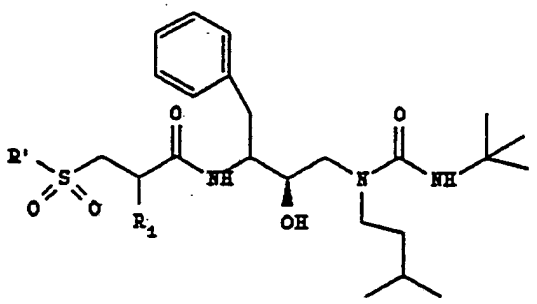
TABLE 12



R
CH_3-
CH_3CH_2-
$CH_3CH_2CH_2-$
$PhCH_2CH_2-$
$PhCH_2-$
$Ph-$
$(CH_3)_2CH-$
$HOCH_2CH_2-$
$C_6H_5CH_2O-\overset{O}{\overset{\|}{C}}CH_2$
$H_2N\overset{O}{\overset{\|}{C}}CH_2-$

$CH_2=CH-CH_2-$

TABLE 13



R'	R_1
CH_3	$-CH(CH_3)_2$

Example 27

Preparation of 2(S)-methyl-3-(methylsulfonyl)propionic Acid.

To a solution of 10g of D-(-)-S-benzoyl-b-mercaptioisobutyric acid t-butyl ester in 20 mL of methanol was bubbled in gaseous ammonia at 0°C. The reaction was allowed to then warm to room temperature, stirred overnight and concentrated under reduced pressure. The resulting mixture of a solid (benzamide) and liquid was filtered to provide 5.21g of a pale oil which then solidified. This was identified as 2(S)-methyl-3-mercaptopropionic aid t-butyl ester.

To a solution of 5.21g of 2(S)-methyl-3-mercaptopropionic acid t-butyl ester in 75 mL of toluene at 0°C was added 4.50g of 1,8-diazabicyclo[5.40]undec-7-ene and 1.94 mL of methyl iodide. After stirring at room temperature for 2.5 h urs, the volatiles w r remov d, ethyl acetat added, washed with dilute hydr chloric acid, wat r, brine, dried and conc ntrated

to afford 2.82g of a pale oil, identified as 2(S)-methyl-3-(thiomethyl)propionic acid t-butyl ester.

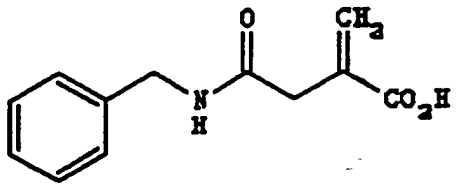
To a solution of 2.82g of 2(S)-methyl-3-(thiomethyl)propionic acid t-butyl ester in 50 mL of acetic acid was added 5.58g of sodium perborate and the mixture heated to 55°C for 17 hours. The reaction was poured into water, extracted with methylene chloride, washed with aqueous sodium bicarbonate, dried and concentrated to afford 2.68g of 2(S)-methyl-3-(methylsulfonyl)propionic acid t-butyl ester as a white solid.

To 2.68g of 2(S)-methyl-3-(methylsulfonyl)propionic acid t-butyl ester was added 20 mL of 4N hydrochlorid acid/dioxane and the mixture stirred at room temperature for 19 hours. The solvent was removed under reduced pressure to afford 2.18g of crude product, which was recrystallized from ethyl acetate/hexane to yield 1.44g of 2(S)-methyl-3-(methylsulfonyl)propionic acid as white crystals.

Example 28

This example illustrates preparation of compounds of Formula IV wherein t is 1.

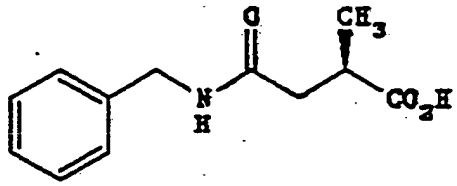
4-N-benzyl itaconamide.



A 500 mL three necked round bottomed flask equipped with a dropping funnel, mechanical stirrer, nitrogen inlet and reflux condenser was charged with itaconic anhydride (33.6g, 0.3 mol) and 150 mL of toluene. This solution was added a solution of benzylamine (32.1g, 0.3 mol) in 50 mL of toluene dropwise over 30 m at r m temperature.

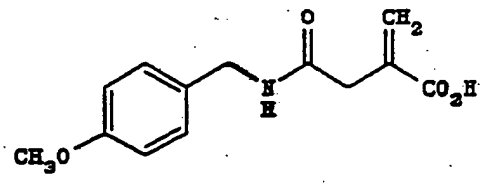
The solution was stirred at this temperature an additional 3h and then the solid product isolated by filtration on a Büchner funnel. The crude product, 64.6g 98%, was recrystallized from 300 mL of isopropyl alcohol to give after two crops 52.1g, 79% of pure product, mp 149-150 °C

2(R)-Methyl 4-N-benzyl succinamide.



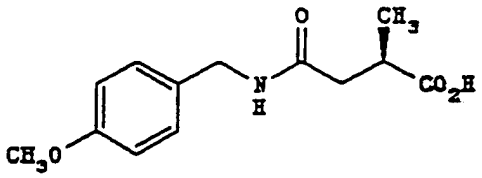
A large Fisher-Porter bottle was charged with the acid from the above reaction (10.95g, 0.05 mol), rhodium (R,R)-DiPAMP (220mg, 0.291 mmol) and 125 mL of degassed methanol. The solution was then hydrogenated at 40 psig for 16h at room temperature. After the hydrogen uptake ceased, the vessel was opened and the solution concentrated *in vacuo* to give a yellow solid, 11.05g, 100%. The product was then taken up in absolute ethanol and allowed to stand whereupon crystals of the desired product formed, 7.98g, 72%, mp 127-129 °C $[a]_D$ @ 25 °C=+14.9° (c=1.332, EtOH), ^1H nmr ($CDCl_3$) 300MHz 7.30(m,5H), 6.80(brs, 1H), 4.41(d, J=5.8Hz, 2H), 2.94(m, 1H), 2.62(dd, J=8.1, 14.9Hz, 1H), 2.33(dd, J=5.5, 14.9Hz, 1H), 1.23(d, J=7.2Hz, 3H).

4-N(4-methoxybenzyl)itaconamide.



A 500 mL three necked round bottomed flask equipped with a dropping funnel, mechanical stirrer, nitrogen inlet and reflux condenser was charged with itaconic anhydride (44.8g, 0.4 mol) and 150 mL of toluene. This solution was added a solution of 4-methoxybenzylamine (54.8g, 0.4 mol) in 50 mL of toluene dropwise over 30 m at room temperature. The solution was stirred at this temperature an additional 2h and then the solid product isolated by filtration on a Büchner funnel. The crude product was recrystallized from ethyl acetate/ethanol to give after two crops 64.8g, 65% of pure product, mp 132-134 °C, ^{1}H nmr ($CDCl_3$) 300MHz 7.09(d, J=9.1Hz, 2H), 6.90(brt, J=5.9Hz, 1H), 6.74(d, J=9.1Hz, 2H), 6.22(s, 1H), 5.69(s, 1H), 4.24(d, J=5.9Hz, 2H), 3.69(s, 3H), 3.15(s, 2H). ^{13}C nmr ($CDCl_3$) 170.52, 169.29, 159.24, 135.61, 131.08, 129.37, 128.97, 114.36, 55.72, 43.37, 40.58.

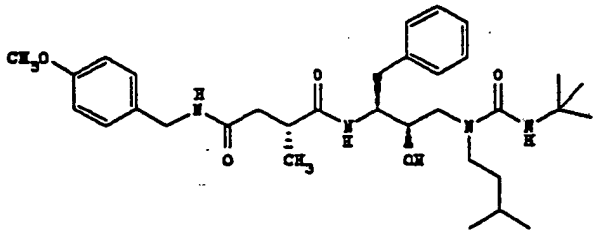
2(R)-Methyl 4-N(4-methoxybenzyl)succinamide.



A large Fisher-Porter bottle was charged with the acid from the above reaction (5.00 g, 0.02 mol), rhodium (R,R)-DiPAMP (110 mg, 0.146 mmol) and 50 mL of degassed methanol. The starting acid was not completely soluble initially, but as the reaction progressed the solution became homogeneous. The solution was then hydrogenated at 40 psig for 16h at room temperature. After the hydrogen uptake ceased, the vessel was opened and the solution concentrated *in vacuo* to give a yellow solid. The crude product was then tak n up in thyl acetate and washed three times with sat. aq. $NaHCO_3$ solution. Th combined aque us extracts were acidified t pH=1 with 3 N HCl and then extracted three times with ethyl acetate.

The combined ethyl acetat extracts were washed with brine, dri d over anhyd. $MgSO_4$, filtered and concentrated to give the expected product as a white solid, 4.81g, 95%. This material was recrystallized from a mixture of methyl ethyl ketone/hexane to give 3.80g, 75% of pure product, $[a]_D$ @ 25 °C=+11.6° (c=1.572, MeOH). ^1H nmr ($CDCl_3$) 300MHz 11.9(brs, 1H), 7.18(d, J=9.2Hz, 2H), 6.82(d, J=9.2Hz, 2H), 6.68(brt, J=5.6Hz, 1H), 4.33(d, J=5.6Hz, 2H), 3.77(s, 3H), 2.92(ddq, J=7.9, 5.4, 7.3Hz, 1H), 2.60(dd, J=5.4, 15.0Hz, 1H), 2.30(dd, J=7.9, 15.0Hz, 1H),1.22(d, J=7.3Hz, 3H).

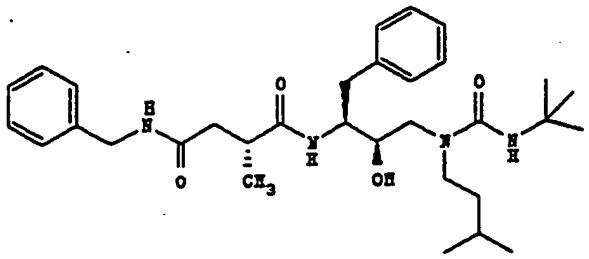
Butanediamide, N'-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-N-4-methoxyphenylmethyl-2-methyl, [1S-[1R*(2R*),2S*]]-



A 50 mL round bottomed flask was charged with 2(R)-methyl 4-N(4-methoxybenzyl)succinamide (588 mg, 2.35 mmol), N-hydroxybenzotriazole (511 mg, 3.34 mmol) and 6 mL of DMF. The solution was cooled to 0° C and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (502 mg, 2.62 mmol) for 20 m. A solution of (2R,3S)-3-amino-1-(3-methylbutyl)-1-[(1,1-dimethyl thyl)amin]carbonyl)-4-phenyl-2-butanol (782 mg, 2.24 mmol) in 2 mL f DMF was added and the s lution stirred at room temperature f r a peri d of 24 h. The soluti n was concentrated *in vacuo* and poured into 50 mL

f 50% sat. aq. $NaHCO_3$, the aqueous phase was extracted with CH_2Cl_2. The organic phase was wash d with 5% citric acid, $NaHCO_3$, brine, dried over anhyd. $MgSO_4$, filtered and concentrated to give an oil that was purified by radial chromatography on SiO_2 eluting with hexane/ethyl acetate to give 790 mg, 59% of pure product as a white foam.

Butanediamide, N'-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-N-phenylmethyl-2-methyl, [1S-[1R*(2R*),2S*]]-



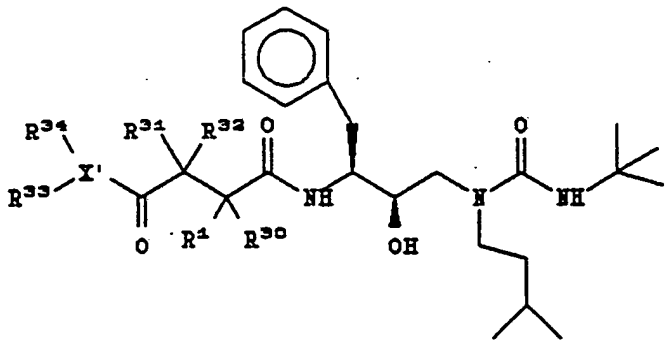
A 50 mL round bottomed flask was charged with 2(R)-methyl 4-N-(benzyl) succinamide (243 mg, 1.1 mmol), N-hydroxybenzotriazole (213 mg, 1.39 mmol) and 3 mL of DMF. The solution was cooled to 0° C and treated with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (228 mg, 1.17 mmol) for 20 m. A solution of (2R,3S)-3-amino-1-(3-methylbutyl)-1-[(1,1-dimethylethyl)amino]carbonyl)-4-phenyl-2-butanol (327 mg, 0.95 mmol) in 2 mL of DMF was added and the solution stirred at room temperature for a period of 24 h. The solution was concentrated *in vacuo* and poured into 50 mL of 50% sat. aq. $NaHCO_3$, th aqu us phase was extracted with CH_2Cl_2. The organic phase was washed with 5% citric acid, $NaHCO_3$, brine, dried over anhyd. $MgSO_4$, filtered and concentrated to give an il that was purified by

flash chromatography on SiO_2 eluting with h xane/ethyl acetat to give 370 mg, 70% of pure product as a whit foam.

Example 29

Following the procedure generally as set forth in Example 28, the compounds shown in Table 14 were prepared.

TABLE 14



R^1	R^{30}	R^{31}	R^{32}	X'	R^{33}	R^{34}
H	H	H	H	N	H	H
H	H	H	H	O	H	-
H	H	H	H	O	CH_3	-
CH_3	H	H	H	N	H	H
CH_3	H	H	H	O	H	-
H	H	CH_3	H	N	H	H
H	H	CH_3	H	O	H	-
CH_3	CH_3	H	H	N	H	H
CH_3	CH_3	H	H	O	H	-
CH_3	CH_3	H	H	O	$CH_2C_6H_4OCH_3$	-
H	H	CH_3	CH_3	N	H	H
H	H	CH_3	CH_3	O	H	-
H	H	CH_3	CH_3	O	$CH_2C_6H_4OCH_3$	-

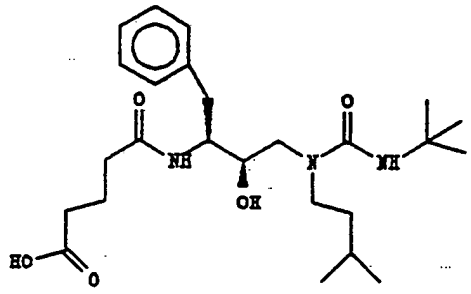
TABLE 14 (Cont'd)

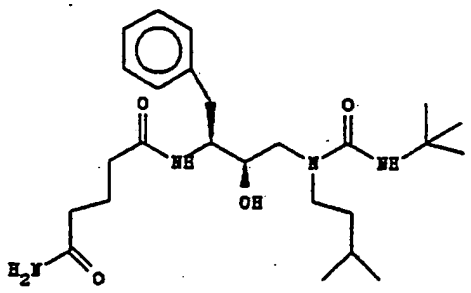
R^1	R^{30}	R^{31}	R^{32}	X'	R^{33}	R^{34}
CH_3	H	CH_3	H	N	H	H
CH_3	H	CH_3	H	N	H	CH_3
CH_3	H	CH_3	H	N	CH_3	CH_3
CH_3	H	CH_3	H	O	H	-
CH_3	H	CH_3	H	N	H	$-CH_2C_6H_5OCH_3$
OH	H	H	H	N	H	H
OH	H	H	H	O	H	-
H	H	OH	H	N	H	H
H	H	OH	H	O	H	-
CH_2	H	H	H	N	H	H
$CH_2C(O)NH_2$	H	H	H	N	H	H
$CH_2C(O)NH_2$	H	H	H	O	H	-
$CH_2C(O)NH_2$	H	H	H	O	CH_3	-
CH_2Ph	H	H	H	N	H	H
CH_3	H	H	H	N	H	
CH_3	H	H	H	N	H	
CH_3	H	H	H	N	H	
CH_3	H	H	H	N	H	
CH_3	H	H	H	N	H	

Example 30

Following the procedure generally as set forth in Example 28, the compounds shown in Table 15 were prepared.

TABLE 15





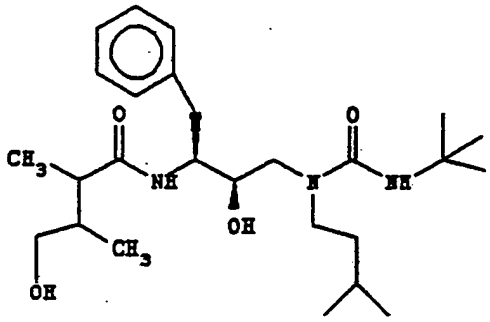
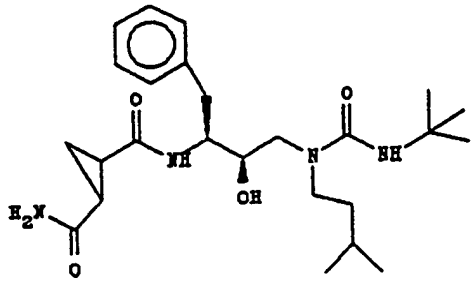


TABLE 15 (Cont'd)



Example 31

Preparation of 3(S)-[N-(2-quinolinylcarbonyl)-L-asparaginyl]amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl).

Part A:

Preparation of N-3(S)-(Benzyloxycarbonyl)-amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl). A solution of 20g (67 mmol) of N-benzyloxycarbonyl-3(S)-amino-1,2-(S)-epoxy-4-phenylbutane in 140 mL of isopropyl alcohol was treated with 83g (952 mmol) of isoamylamine and refluxed for one hour. The solution was cooled, concentrated, hexane added and the resulting solid filtered to afford 22.4g of the desired product.

Part B:

Preparation of N-3(S)-(Benzyloxycarbonyl)-amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl)-N-(t-butyloxycarbonyl). To a solution of 22.4g (58.3 mmol) of product from Part A above, 6.48g (64.1 mmol) of triethylamine and 150 mg of N,N-dimethyl-4-aminopyridine in 200 mL of tetrahydrofuran at 0°C was added 12.7g (58.3 mm l) of di-t-butylpyrocarbonate in 10 mL f THF. Aft r 3.5 hours at ro m temperature, th v latil s were rem ved, ethyl acetate added and washed with 5% citric acid, sat d $NaHCO_3$, dri d and concentrated

to afford 30g f crude product. Chromatography on silica gel using 20% ethyl acetate/h xane afforded 22.5g (79%) of the desired product.

Part C:

Preparation of N-3(S)-[N-benzyloxycarbonyl-L-asparaginyl]amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl)-N-(t-butyloxycarbonyl). A solution of 22.5g of product from Part B above in 200 mL of ethanol was hydrogenated over 5.9g of 10% palladium-on-carbon under 50 psig hydrogen for one hour. The catalyst was filtered and the solvent removed under reduced pressure to afford 15.7g of free amine. This was dissolved in 130 mL of DMF and 4.54g (44.9 mmol) of N-methylmorpholine an added to a mixture of 13.3g (49.9 mmol) N-benzyloxy-carbonyl-L-asparagine, 11.5g (74.9 mmol) of N-hydroxybenzotriazole and 10.5g (54.9 mmol) of EDCl in 120 mL of DMF at 0°C, which had been preactivated for one hour prior to the addition. The mixture was stirred for 2 hours at 0°C and then for 12 hours at room temperature. The reaction was poured into 1L of sat d aqueous sodium bicarbonate, the solid collected, dissolved in ethyl acetate, washed with water, sat d sodium bicarbonate, 5% citric acid and brine, dried and concentrated to afford 16.7g of the desired product.

Part D:

Preparation of N-3(S)-[N-(2-quinolinylcarbonyl)-L-asparaginyl]amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl)-N-(t-butyloxycarbonyl). A solution of 16.7g (28.0 mmol) of product from Part C in 250 mL of methanol was hydrogenated over 6.0g of 10% palladium-on-carbon and under 50 psig hydrogen for one hour. The catalyst was filtered and th s luti n c ncentrated to afford 10.0g of free amine. This was dissolved in 100 mL f methylene chloride, 4.35g (43 mmol) of N-methylmorpholine was added followed by 5.53g (20.5

mmol) of quinolin -2-carboxylic acid, N-hydroxysuccinimid ester. This was stirred at room temperature overnight, the solvent removed, ethyl acetate added and washed with 5% citric acid, sat d sodium bicarbonate, brine, dried and concentrated to afford 14g of crude product. Recrystallization from ethyl acetate and hexane afforded 10.5g (83%) of desired product.

Part E:

Preparation of N-3(S)-[N-(2-quinolinyl-carbonyl)-L-asparaginyl]amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl). To 80 mL of 4N hydrochloric acid in dioxane was added 9.17g (14.8 mmol) of product from Part D above. After one hour, the product becomes gummy. The solvents were removed, diethyl ether added and removed and the residue dissolved in 20 mL of methanol. This solution was added to 400 mL of sat d aqueous sodium bicarbonate, the solids collected, washed with acetone and hexane and dried in vacuo over P_2O_5 to afford 4.75g of the desired product.

Example 32A

Preparation of Benzyl 2,2,3(R)-trimethylsuccinate

Part A:

Preparation of Methyl (S)-lactate, 2-methoxy-2-propyl ether. To a mixture of methyll(s)-(-)-lactate (13.2g, 100 mmol) and, 2-methoxypropene (21.6g, 300 mmol) in CH_2Cl_2 (150 ml) was added $POCl_3$ (7 drops) at r.t. and the resulting mixture was stirred at this temperature for 16 hours. After the addition of Et_3N (10 drops), the solvents were removed in vacuo to give 20.0g of (98%) desired product.

Part B:

Preparation of 2(S)-hydroxypropanal, 2-methoxy-2-propyl ether. To a solution of compound from Part A (20.0g) in CH_2Cl_2 (100 ml) was added DIBAL (65 ml

of 1.5M solution in toluene, 97.5 mmol) dropwise at -78°C for 45 min., then stirring was continued at the temperature for another 45 min. To this cold solution was added MeOH (20 ml), saturated NaCl solution (10 ml) and allowed the reaction mixture to warm up to r.t. and diluted with ether (200 ml), $MgSO_4$ (150g) was added and stirred for another 2 h. The mixture was filtered and the solid was washed twice with ether. The combined filtrates were rotavaped to afford 11.2g (78%) of the desired aldehyde.

Part C:

Preparation of 2(S)-hydroxy-cis-3-butene, 2-methoxy-2-propyl ether. To a suspension of ethyltriphenylphosphonium bromide (28g, 75.5 mmol) in THF (125 ml) was added KN $(TMS)_2$ (15.7g, 95%, 75 mmol) in portions at 0°C and stirred for 1 h at the temperature. This red reaction mixture was cooled to -78°C and to this was added a solution of aldehyde from Part B (11g, 75 mmol) in THF (25 ml). After the addition was completed, the resulting reaction mixture was allowed to warm up to r.t. and stirred for 16 h. To this mixture was added saturated NH_4Cl (7.5 ml) and filtered through a pad of celite with a thin layer of silica gel on the top. The solid was washed twice with ether. The combined filtrates were concentrated in vacuo to afford 11.5g of crude product. The purification of crude product by flash chromatography (silica gel, 10:1 Hexanes/EtoAc) affording 8.2g (69%) pure alkene.

Part D:

Preparation of 2(S)-hydroxy-cis-3-butene. A mixture of alkene from Part C (8.2g) and 30% aqueous acetic acid (25 ml) was stirred at r.t. for 1 hour. To this mixture was added $NaHCO_3$ slowly to the pH ~ 7, then extracted with ether (10 ml x 5). The combined eth r solutions were dri d (Na_2SO_4) and filter d. The filtrate was distilled t rem ve the ether to give 2.85g (64%) pure alcohol, m/e=87(M+H).

Part E:

Preparation of 2,2,3( )-trimethyl-hex-(trans)-4-enoic acid. To a mixture of alcohol from Part D (2.5g, 29 mmol) and pyridine (2.5 ml) in CH_2Cl_2 (60 ml) was added isobutyryl chloride (3.1g, 29 mmol) slowly at 0°C. The resulting mixture was stirred at r.t. for 2 hours then washed with H_2O (30 ml x 2) and sat. NaCl (25 ml). The combined organic phases were dried (Na_2SO_4), concentrated to afford 4.2g (93%) ester 2(S)-hydroxy-cis-3-butenyl isobutyrate. This ester was dissolved in THF (10 ml) and was added to a 1.0M LDA soln. (13.5 ml of 2.0M LDA solution in THF and 13.5 ml of THF) slowly at -78°C. The resulting mixture was allowed to warm up to r.t. and stirred for 2 h and diluted with 5% NaOH (40 ml). The organic phase was separated, the aqueous phase was washed with Et_2O (10 ml). The aqueous solution was collected and acidified with 6N HCl to pH = 3. The mixture was extracted with ether (30 ml x 3). The combined ether layers were washed with sat. NaCl (25 ml), dried (Na_2SO4) and concentrated to afford 2.5g (60%) of desired acid, m/e=157(M+H).

Part F:

Preparation of benzyl 2,2,3(S)-trimethyl-trans-4-hexenoate.A mixture of acid from Part E (2.5g, 16 mmol), BnBr (2.7g, 15.8 mmol), K_2CO_3 (2.2g, 16 mmol), NaI (2.4g) in acetone (20 ml) was heated at 75°C (oil bath) for 16 h. The acetone was stripped off and the residue was dissolved in H_2O (25 ml) and ether (35 ml). The ether layer was separated, dried (Na_2SO_4) and concentrated to afford 3.7g (95%) of benzyl ester, m/e=247(M+H).

Part G:

Preparation of benzyl 2,2,3(R)-trimethylsuccinate. To a well-stirred mixture of $KMnO_4$ (5.4g, 34, 2 mm l), H_2O (34 ml), CH_2Cl_2 (6 ml) and b nzyltriethylammonium chloride (200 mg) was added a soluti n of ester from Part P (2.1g, 8.54 mmol) and acetic acid (6 ml) in CH_2Cl_2 (28 ml) slowly at 0°C. The

resulting mixture was stirred at the temperature for 2 h then r.t. for 16 h. The mixture was cooled in an ice-water bath, to this was added 6N HCl (3 ml) and solid $NaHSO_3$ in portions until the red color disappeared. The clear solution was extracted with CH_2Cl_2 (30 ml x 3). The combined extracts were washed with sat. NaCl solution, dried (Na_2SO_4) and concentrated to give an oil. This oil was dissolved in Et_2O (50 ml) and to this was added sat. $NaHCO_3$ (50 ml). The aqueous layer was separated and acidified with 6N HCl to pH ~ 3 then extracted with Et_2O (30 ml x 3). The combined extracts were washed with sat. NaCl solution (15 ml), dried (Na_2SO_4) and concentrated to afford 725 mg (34%) of desired acid, benzyl 2,2,3(R)-trimethylsuccinate, m/e=251(M+H).

Example 32B

Part A:

Preparation of Butanediamide, N¹-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2,3,3-trimethyl-[1S-,[1R*(2S*),2S*]]-

To a well-stirred solution of acid benzyl 2,2,3(R)-trimethylsuccinate (225 mg, 0.9 mmol) in DMF (1.0 ml) was added HOBt (230 mg, 1.5 mmol). The clear reaction mixture was then cooled to 0°C, to this was added EDC (210 mg, 1.1 mmol) and stirred for 1 h at the temperature. To this cold mixture was added a powder of (350 mg, 1.0 mmol) and DMF (0.5 ml). The resulting reaction mixture was stirred for 2 h at 0°C and 16 h at r.t. After the removal of DMF (≤ 40°C), a solution of 60% sat. $NaHCO_3$ (10 ml) was added. This mixture was extracted with EtOAc (10 ml x 2). The extracts were combined and washed with sat. $NaHCO_3$ (10 ml x 2), 5% citric acid (10 ml x 2), H_2O (10 ml), sat. NaCl (10 ml) and dried (Na_2SO_4) th n conc ntrated t afford 512 mg (98%) of desired product Butan ic Acid, 4-[[3-[[[(1,1-dim thylethyl)amin]carb nyl](3-methylbutyl)ami]-2-hydroxy-1-(phenylmethyl)pr pyl]amino]-2,2,3-trimethyl-

4-oxo, [1S-[1R*(3S*),2S*]]-benzyl ester as a white solid, m/ =582(M+H).

Part B:

A mixture of benzyl ester 10 (480 mg, 0.825 mmol), 10% Pd/C (450 mg) in MeOH (25 ml) was hydrogenated (H_2, 50 psi) for 1/2 h at r.t. The mixture was filtered and the solid was washed with MeOH (10 ml). The collected filtrates were concentrated to afford a crude acid as a white solid. The crude acid was dissolved in Et_2O-EtOAc (10:1, 25 ml) and the solution was washed with sat. $NaHCO_3$ (25 ml) then 5% NaOH (10 ml). The combined aqueous layers were cooled to 0°C and acidified with concentrated HCl (Co_2) to pH ~ 1 then extracted with Et_2O-EtOAC (10:1, 25 ml x 3). The combined extracts were washed with sat. NaCl (15 ml), dried (Na_2SO_4) and concentrated to afford 307 mg (75.7%) of pure acid Butanoic acid, 4-[[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo-,[1S-[1R*(3S*),2S*]]-, as a white solid, m/e=491(M+H).

Part C:

Butanoic acid, 4-[[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-2,2,3-trimethyl-4-oxo-,[1S-[1R*(3S*),2S*]]-, as a white solid, m/e=491(M+H).

To a well-stirred solution of the acid 11 (245 mg, 0.5 mmol) in DMF (0.5 ml) was added HOBt (153 mg, 1.0 mmol) and EDC (143 mg, 0.75 mmol) at 0°C. After stirring at 0°C for 2 h, NH_4OH (0.63 ml of 28% NH_4OH, 5 mmol) was added and stirred at 0°C for 2 h, r.t. for 16 h. The removal of DMF (≤ 40°C) gave a white solid. The purification of the crud pr duct by flash chromat graphy (silica gel, 5% MeOH/CH_2Cl_2) gave 172 mg (70%) of pur amide 12 as a white s lid, m/e=491(M+H).

Example 33

Preparation of methyl 2,2-dimethyl-3-methyl succinate, (R) and (S) isomers.

Part A:

Preparation of methyl 2,2-dimethyl-3-oxo-butanoate. A 250 ml RB flask equipped with magnetic stir bar and N_2 inlet was charged with 100 ml dry THF and 4.57g (180 mmol) of 95% NaH. The slurry was cooled to -20°C and 10g (87 mmol) methyl acetoacetate was added dropwise followed by 11.3 ml (181 mmol) CH_3I. The reaction was stirred at 0°C for 2 hours and let cool to room temperature overnight. The reaction was filtered to remove NaI and diluted with 125 ml Et_2O. The organic phase was washed with 1x100 l 5% brine, dried and concentrated in vacuo to a dark golden oil that was filtered through a 30g plug of silica gel with hexane. Concentration in vacuo yielded 10.05g of desired methyl ester, m/e= ? as a pale yellow oil, suitable for use without further purification.

Part B:

Preparation of methyl 2,2-dimethyl-3-O-(trifluoromethanesulfonate)-but-3-enoate. A 250 ml RB flask equipped with magnetic stir bar and N_2 inlet was charged with 80 l by THF and 5.25 ml (37.5 mmol) diisopropylamine was added. The solution was cooled to -25°C (dry ice/ethylene glycol) and 15 ml (37.5 mmol) of 2.5 M nbuLi in hexanes was added. After 10 minutes a solution of 5g (35 mmol) 1 in 8 ml dry THF was added. The deep yellow solution was stirred at -20°C for 10 min. then 12.4g N-phenyl bis(trifluoromethanesulfonimide) (35 mmol) was added. The reaction was stirred @ -10°C for 2 hours, concentrated in vacuo and partioned between EA and sat. bicarb. The combined organic phase was washed with bicarb, brine and conc. to an amber il that was filtered through 60g silica gel plug with 300 l 5% EA/H. C nc. in vacuo yield d 9.0g light yellow oil that was diluted with 65 ml EA and wash d with 2x50 ml 5% aq

K_2CO_3, 1x10 l brin , dri d over Na_2SO_4 and conc. in vacuo to yield 7.5g (87%) vinyl triflate, (m/e=277(M+H) suitable for use without further purification.

Part C:

Preparation of methyl 2,2-dimethyl-3-carboxyl-but-3-enoate. A 250 ml Fisher Porter bottle was charged with 7.5g (27 mmol) 2, 50 ml dry DMF, 360 mg (1.37 mmol) triphenyl phosphine and 155 mg (.69 mmol) $Pd^{II}(OAc)_2$. The reaction mixture was purged twice with N_2. then charged with 30 psi CO. Meanwhile a solution of 20 ml dry DMF and 7.56 ml (54 mmol) NEt_3 was cooled to 0°C to this was added 2.0g (43 mmol) of 99% formic acid. The mixture was swirled and added to the vented Fisher Porter tube. The reaction vessel was recharged to 40 psi of CO and stirred 6 hours @ room temperature. The reaction mixture was concentrated in vacuo and partionned between 100 l EA/75 ml 5% aq K_2CO_3. The aqueous phase was washed with 1x40 l additional EA and then acidified with conc. HCl/ice. The aqueous phase was extracted with 2x70 l EA and the organics were dried and conc. to yield 3.5g (75%) white crystals, mp 72-75°C, identified as the desired product (m/e=173(M+H).

Part D:

Preparation of methyl 2,2-dimethyl-3-methylsuccinate, isomer #1. A steel hydrogenation vessel was charged with 510 mg (3.0 mmol) acrylic acid, 3, and 6 mg Ru $(acac)_2$ (R-BINAP) in 10 ml degassed MeOH. The reaction was hydrogenated at 50 psi/room temperature for 12 hours. The reaction was then filtered through celite and conc. to 500 mg clear oil which was shown to be a 93:7 mixture of isomer #1 and #2, respectively as determined by GC analysis using a 50 M β-cyclodextrin column: 150°C - 15 min. then ramp 2°C/min.; isomer #1, 17.85 min., isomer #2, 18-20 min.

Part E:

Preparati n f methyl 2,2-dimethyl-3-methylsuccinate, Isomer #2. A steel hydr genation vess l was charged with 500 mg (2.9 mm l) acrylic acid,

3, and 6 mg Ru(OAc) (acac)(S-BINAP) in 10 ml degassed MeOH. The reaction was hydrogenated at 50 psi/room temperature f r 10 hours. The reaction was filtered through celite and concentrated in vacuo to yield 490 mg of product as a 1:99 mixture of isomers #1 and #2, respectively, as determined by chiral GC as above.

Example 34

Preparation of 3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2(R)-hydroxy-1(S)-(phenylmethyl)propylamine, 1.

Part A:

To a solution of 75.0g (0.226 mol) of N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of tetrahydrofuran at -2°C, was added 13.17g (0.348 mol, 1.54 equiv.) of solid sodium borohydride over one hundred minutes. The solvents were removed under reduced pressure at 40°C and the residue dissolved in ethyl acetate (approx. 1L). The solution was washed sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and then saturated sodium chloride solution. After drying over anhydrous magnesium sulfate and filtering, the solution was removed under reduced pressure. To the resulting oil was added hexane (approx. 1L) and the mixture warmed to 60°C with swirling. After cooling to room temperature, the solids were collected and washed with 2L of hexane. The resulting solid was recrystallized from hot ethyl acetate and hexane to afford 32.3g (43% yield) of N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp 150-151°C and $M+Li^+ = 340$.

Part B:

To a solution of 6.52g (0.116 mol, 1.2 equiv.) of potassium hydr xide in 968 mL of absolute ethan l at room temperatur , was added 32.3g (0.097 m l) of N-CBZ-3(S)-amino-1-chl r -4-phenyl-2(S)-butanol. After stirring for fifteen minutes the solvent was removed

under reduced pressure and the solids dissolved in methylene chloride. After washing with water, drying over magnesium sulfate, filtering and stripping, one obtains 27.9g of a white solid. Recrystallization from hot ethyl acetate and hexane afforded 22.3g (77% yield) of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane, mp 102-103°C and MH^+ 298.

Part C:

A solution of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane (30.1g, 0.10 mol) and 165mL of isoamylamine in 150 mL of isopropyl alcohol was heated to reflux for 2.5 hours. The solution was cooled to room temperature, concentrated *in vacuo* and then recrystallized. The product was isolated by filtration and from ethylacetate/hexane to afford 31.7g (81%) of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]N-isoamylamine.

Part D:

A solution of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenyl butyl], N-isoamylamine in 10 ml of tetrahydrofuran was treated with tert-butylisocyanate (267 mg, 2.70 mmol) at room temperature for 5 minutes. The solvent was removed *in vacuo* and replaced with ethyl acetate. The ethyl acetate solution was washed with 5% citric acid, water, and brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give 1.19g, 97% of N-benzyloxycarbonyl-3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2(R)-hydroxy-1(S)-(phenylmethyl)propylamine. MH^+ m/z = 470.

Part E:

A solution of (37.3g, 77 mmol) of product from Part D in 100 mL of methanol was hydrogenated over 10% palladium-on-carbon for 4 hours to afford 26.1g of the desired final pr duct 1.

Example 35

Preparation of Butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, [1S-[1R*, 2S*]]-.

Part A:

To a solution of 102mg (0.29 mmol) of 1 and 70 mg (0.89 mmol) of pyridine in 2 mL of methylene chloride was added 29 mg (0.29 mmol) of succinic anhydride. After 2 hours, ethyl acetate was added and then extracted with saturated NaHCO. The aqueous layer was acidified, reextracted with ethyl acetate, washed with saturated brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford 78 mg (60%) of butanoic acid, 4-[[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]amino-4-oxo-, [1S-[1R*, 2S*]]-.

Part B:

This was activated with EDC and N-hydroxybenzotriazole in N,N-dimethylformamide and then reacted with ammonia to generate the desired final compound.

Example 36

Part A:

To a solution of 4.60g (24.7 mmol) of trans-diethyl 1,2-cyclopropanedicarboxylatease in 100 mL of 50:50 v:v tetrahydrofuran/water was added 1.24g (29.6 mmol) of lithium hydroxide. After 17 hours, the tetrahydrofuran was removed *in vacuo*, the water layer washed with ethyl acetate, acidified with IN hydrochloric acid and reextracted with ethyl acetate. The organic layer was dried and stripped to afford 2.1g of crude product. After recrystallization from diethyl ether/hexane and then methylene chloride/hexane one obtains 1.1g (28%) of trans-m noethyl 1,2-cyclopr panedicarb xylate, m/e = 159 (M + H).

Part B:

To a solution of 297 mg (1.87 mmol) of trans-monoethyl 1,2-cyclopropanedicarboxylate and 429 mg (2.8 mmol) N-hydroxybenzotriazole (HoBT) in 3 mL of anhydrous N,N-dimethylformamide (DMF) at 0°C was added 394 mg (2.0 mmol) of 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (EDC). After 30 min. a solution of 591 mg (1.7 mmol) of 1 in 2 mL DMF and 171 mg (1.69 mmol) of N-methylmorpholine (NMM) was added. After 2 hours at 0°C, the reaction was stirred at RT overnight, poured into water, extracted with ethyl acetate, washed with water, 5% aq. citric acid, sat'd $NaHCO_3$, sat'd brine, dried and stripped to afford 771 mg of crude product. This was chromatographed on silica gel using 5-20% methanol/methylene chloride to afford 670 mg (80%) of cyclopropane carboxylic acid, 2-[[[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]carbonyl]-, ethyl ester; m/e = 490 (M + H).

Part C:

To a solution of 658 mg (1.32 mmol) of product from part B in 5 mL of 50:50 THF/water was added 66 mg (1.58 mmol) of lithium hydroxide. After 19 hours, the THF was removed *in vacuo*, the water washed with ethyl acetate, acidified and reextracted with ethyl acetate. The organic layer was dried and stripped to afford 328 mg (54%) of the corresponding acid, m/e = 462 (M + H).

Part D:

To a solution of 304 mg (0.66 mmol) of product from part C, 151 mg (0.99 mmol) HoBT in 2.2 mL DMF at 0°C was added 139 mg (0.73 mmol) EDCl. After 30 min. at 0°C, 1.1 mL of conc. aqueous ammonia was added. After stirring at 0°C for 2 hours and RT for 20 hours, the reaction was p ured into sat'd brin and extract d with ethyl acetate. After washing with sat'd $NaHCO_3$, sat'd brine, drying and stripping, n btains 141 mg f crude

product. This was chromatographed on silica gel with 1-5% methanol/methylene chloride to afford 40 mg (13%) of the desired final product, m/e = 561 (M + H).

Example 37

Preparation of trans-but-2-enediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, [1S-[1R*, 2S*].

Part A:

To a solution of 137 mg (0.95 mmol) fumaric acid monoethyl ester in 1 mL of DMF at 0°C was added 183 mg (0.95 mmol) EDCl. After 15 minutes, a solution of 333 mg (0.95 mmol) of 1 in 1 mL DMF was added and the reaction stirred for 14 hours at RT. Ethyl acetate was added and extracted with sat'd brine, 0.2 n HCl, sat'd $NaHCO_3$, dried and stripped to afford 0.32g of crude product. Chromatography on silica gel using 0-50% ethyl acetate/hexane afforded 0.26g (58%) of but-2-enoic acid, 4-[[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-4-oxo-, [1S-[1R*, 2S*]]-, ethyl ester, m/e = 476 (M + H).

Part B:

To a solution of 26.6 mg (0.56 mmol) of product from part A in 3 mL of 50:50 THF/water was added 34 mg (0.82 mmol) of lithium hydroxide and the reaction stirred at RT for 1 hour. The THF was removed *in vacuo*, the aqueous layer acidified with 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried and stripped to afford 233 mg (93%) of trans-but-2-enoic acid, 4-[[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-4-oxo-, [1S-[1R*, 2S*]-, m/e = 448 (M + H).

Part C:

To a solution of 225 mg (0.50 mmol) of the product from part B in 1 mL of DMF was added 95 mg (0.50 mmol) EDCl. After 15 minutes at RT, 0.50 mL of conc. aqueous ammonia was added and the reaction stirred for

15 hours. Ethyl acetate was added and washed with 0.2N HCl, brine, dried and stripped to afford 170 mg of crude product. After chromatography on silica gel using 0-40% methanol/methylene chloride, one obtains 50 mg (22%) of trans-but-3-enediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, [1S-[1R*, 2S*]-, m/e = 447 (M + H).

Example 38

Preparation of butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl-2-methyl-, [1S-[1R*(2S*), 2S*]-.

Part A:

To a suspension of 24.7g (0.22 mol) of itaconic anhydride in 100 mL of anhydrous toluene at reflux under a nitrogen atmosphere was added dropwise over 30 minutes 23.9g (0.22 mol) of benzyl alcohol. The insoluble material dissolved to provide a homogeneous solution which was refluxed for 1.5 hours. The solution was cooled to RT, then in an ice bath and the resulting white precipitate collected by filtration to afford 24.8g (51%) of 4-benzyl itaconate.

Part B:

To a solution of 2.13g (9.5 mmol) of the product from part A in 12 mL of methylene chloride at 0°C was added 4.02g (29.1 mmol) of para-methoxybenzyl alcohol, 605 mg (4.95 mmol) of N,N-dimethyl 4-aminopyridine, 128 mg of N,N-dimethyl 4-aminopyridine hydrochloride salt and then 2.02g (4.7 mmol) dicyclohexylcarbodiimide (DCC). After stirring at 0°C for 1 hour and then RT for 2 hours, the precipitate was collected and discarded. The filtrate was washed with 0.5 N HCl, sat'd $NaHCO_3$, dried and stripped to afford 4.76g of crude product. This was chromatographed on silica gel using 0-50% ethyl acetate/hexane to afford 1.24g of pure 4'-methoxybenzyl-4-benzylitaconate, MH^+ m/z =

Part C:

A solution of 1.24g (3.65 mmol) of product from part B and 20 mg of [(R,R)-Dipamp)cyclooctadienylrhodium] tetrafluoroborate in 30 mL of methanol was thoroughly degassed, flushed with nitrogen and then hydrogen and then stirred under 50 psig of hydrogen for 15 hours. The solution was filtered and stripped, dissolved in methylene chloride and washed with sat'd $NaHCO_3$, dried and stripped to afford 0.99g of a brown oil. This was then dissolved in 40 mL of methylene chloride, 3 mL of trifluoroacetic acid added and the solution stirred at RT for 3.5 hours. Water was added and separated and the organic layer extracted with sat'd $NaHCO_3$. The aqueous layer was acidified and reextracted with ethyl acetate, separated and the organic layer washed with brine, dried and stripped to afford 320 mg (50%) of 2(R)-methyl-4-benzylsuccinic acid.

Part D:

To a solution of 320 mg (1.44 mmol) of product from part C and 314 mg (2.05 mmol) HoBT in DMF at 0°C was added 303 mg (1.58 mmol) of EDCl. After stirring for 30 minutes, a solution of 467 mg (1.34 mmol) of 1 in 4 mL of DMF was added. After stirring for 1 hour at 0°C and 14 hours at RT, ethyl acetate was added and washed with sat'd $NaHCO_3$, 5% aqueous citric acid, dried and stripped to afford 0.97g of crude product. This was chromatographed on silica gel using 0-10% ethyl acetate/hexane to afford 420 mg of pure butanoic acid, 4-[[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-3-methyl-4-oxo-, [1S-[1R*(3S*), 2S*]-, benzyl ester.

Part E:

A solution f 150 mg (0.27 mmol) of product fr m part D in 15 mL of m thanol was hydrogenated over 10% palladium on carbon under 50 psig hydr gen for 17 h urs. The reacti n was filtered and stripped to afford

125 mg (100%) of butanoic acid, 4-[[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-3-methyl-4-oxo-, [1S-[1R*(3S*), 2S*]-.

Part F:

To a solution of 125 mg (0.27 mmol) of product from part E and 65 mg (0.42 mmol) of HoBT in 5 mL of DMF at 0°C was added 59 mg (0.31 mmol) of EDCl. After 30 min. at 0°C, 1 mL of conc. aqueous ammonia was added. After stirring at 0°C for 2 hours and RT fro 15 hours, ethyl acetate was added and washed with sat'd $NaHCO_3$, 5% aqueous citric acid, dried and stripped to afford 90 mg of crude product. This was recrystallized from ethyl acetate/hexane to afford 40 mg (32%) of pure butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl, [1S-[1R*(2S*), 2S*]-.

Example 39

Preparation of butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl, [1S-[1R*(2R*), 2S*]-.

Part A:

A solution of 1.41g (4.1 mmol) of 4'-methoxybenzyl 4-benzylitaconate and 25 mg of [(S,S-Dipamp)cyclooctadienylrhodium]tetrafluoroborate in 20 mL of methanol was thoroughly degassed, flushed with nitrogen and then hydrogen and then stirred under 40 psig hydrogen for 72 hours. The solution was filtered and concentrated to provide 1.34g of a brown oil. This was dissolved in 40 mL of methylene chloride and 3 mL of trifluoroacetic acid was added. AFter stirring for 4 hours, water was added, separated and the organic layer extracted with sat'd $NaHCO_3$. The aqueous layer was separated, reacidified, xtracted with ethyl acetate which was separated, washed with brine, dri d and

stripped to afford 440 mg of 2(S)-methyl-4-benzylsuccinic acid.

Part B:

To a solution of 440 mg (1.98 mmol) of the product from part A and 437 mg (2.86 mmol) of HoBT in 9 mL of DMF at 0°C was added 427 mg (2.23 mmol) of EDCl. After 30 minutes at 0°C, a solution of 653 mg (1.87 mmol) of 1 in 3 mL DMF was added. After 1 hour at 0°C and 15 hours at RT, ethyl acetate was added, extracted with sat'd $NaHCO_3$, 5% aqueous citric acid, dried and concentrated to afford 0.98g of crude product. Chromatography on silica gel using 0-10% ethyl acetate afforded 610 mg (59%) of pure butanoic acid, 4-[[3-[[[(1,1-dimethylethyl)-amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-3-methyl-4-oxo-, [1S-[1R*(3R*), 2S*], benzyl ester.

Part C:

A solution of 310 mg (0.56 mmol) of the product from part B in 20 mL of methanol was hydrogenated over 20 mg of 10% palladium on carbon under 50 psig hydrogen for 19 hours. The solution was filtered and concentrated to afford 220 mg (85%) of butanoic acid, 4-[[3-[[[(1,1-dimethylethyl)-amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-3-methyl-4-oxo-, [1S-[1R*(3R*), 2S*].

Part D: To a solution of 190 mg (0.41 mmol) of the product from part C and 90 mg (0.58 mmol) HoBT in 5 mL of DMF at 0°C, was added 88 mg (0.46 mmol) of EDCl. After 30 minutes at 0°C, 2 mL of conc. aqueous ammonia was added. After 1 hour at 0°C and 15 hours at RT, ethyl acetate was added, washed with sat'd $NaHCO_3$, 5% aqueous citric acid, dried and conc ntrated to afford crude product. Recrystallization fr m ethyl acetate/hexan afford d 20 mg (11%) of butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-

methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2-methyl, [1S-[1R*(2R*), 2S*]-.

Example 40

Preparation of butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-methyl-, [1S-[1R*(3S*), 2S*]-.

Part A: In a similar manner to the procedure used above, p-methoxybenzyl alcohol was reacted with itaconic anhydride in refluxing toluene to provide 4-(p-methoxybenzyl)itaconate.

Part B: To a solution of 3.30g (13.2 mmol) of the product from part A in 17 mL of toluene, was added 2.08g (13.7 mmol) of 1,8-diazabicyclo[5.40]undec-7-enc and then 2.35g (13.7 mmol) of benzyl bromide. After 2 hours, the solution was filtered and the filtrate washed with sat'd $NaHCO_3$, 3N HCl, brine, dried and concentrated to afford 3.12g of an oil. After chromatography on silica gel using 0-5% ethyl acetate/hexane one obtains 2.19g (49%) of benzyl 4-(4-methoxybenzyl)itaconate.

Part C:

A solution of 1.22g (3.6 mmol) of product from part B and 150 mg of [((R,R-Dipamp))cyclooctadienylrhodium] tetrafluoroborate in 15 mL of methanol was thoroughly degassed, flushed with nitrogen and then hydrogen and hydrogenated under 50 psig for 16 hours. The solution was filtered and concentrated to afford 1.2g of a brown oil. This was dissolved in 5 mL of methylene chloride and 5 mL of toluene and 3 mL of trifluoroacetic acid was added. After 4 hours, the solvents were removed *in vacuo*, the residue dissolved in methylene chloride, which was then extracted with sat'd $NaHCO_3$. After s paration, the aqueous layer was acidified, reextracted with methylene chloride which was then dried and conc ntrated to afford 470 mg (60%) of 3(R)-methyl-4-benzylsuccinic acid.

Part D:

To a solution of 470 mg (2.11 mmol) of product from part C and 463 mg (3.03 mg) of HoBT in 5 mL of DMF at 0°C was added 451 mg (2.35 mmol) of EDCl. After 30 min. at 0°C, a solution of 728 mg (2.08 mmol) of 1 in 3 mL of DMF was added. After stirring at 0°C for 1 hour and 15 hours at RT, ethyl acetate was added and extracted with sat'd $NaHCO_3$, 5% aqueous citric acid, brine, dried and concentrated to give 930 mg of crude product chromatography on silica gel using 0-10% ethyl acetate/hexane one obtains 570 mg (50%) of butanoic acid, 4-[[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-2-methyl-4-oxo-, [1S-[1R*(2S*), 2S*]-, benzyl ester.

Part E:

The product was hydrogenated in methanol using 10% palladium on carbon under 40 psig of hydrogen to afford butanoic acid, 4-[[3-[[[(1,1-dimethylethyl)amino]carbonyl]-(3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]amino]-2-methyl-4-oxo-, [1S-[1R*(2S*), 2S*]-.

Part F:

To a solution of 427 mg (0.92 mmol) of product from part E and 210 mg (1.37 mmol) in 3 mL of DMF at 0°C was added 196 mg (1.02 mmol) of EDCl. After 30 min. at 0°C, 2 mL of conc. aqueous ammonia was added. After 1 hour at 0°C and 15 hours at RT, ethyl acetate was added and then extracted with sat'd $NaHCO_3$, brine, dried and concentrated to afford crude product. Recrystallization from ethyl acetate/hexane afforded 50 mg (12%) of butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-methyl-, [1S-[1R*(3S*), 2S*]-.

Example 41

Preparation of butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-3-methyl-, [1S-[1R*(3R*), 2S*]-.

This was prepared in an identical manner to the previous example except that the asymmetric hydrogenation step was done in the presence of [((S,S-dipamp)cyclooctadienyl)rhodium]-tetrafluoroborate as catalyst.

Example 42

Preparation of butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, [1S-[1R*(2S*, 3R*), 2S*]], and [1S-[1R*(2R*, 3S*), 2S*]].

Part A:

To a solution of 863 mg (5.91 mmol) of meso-2,3-dimethylsuccinic acid in 7 mL of DMF at RT was added 1.13g (5.91 mmol) of EDCl. After 15 minutes, a solution of 2.07g (5.91 mmol) of 1 and 1.4 mL of pyridine in 7 mL of anhydrous methylene chloride was added. After 11 hours, ethyl acetate was added and washed with 0.2N HCl, brine, dried and concentrated to afford 2.73g (97%) of a 1:1 mixture of diastereomeric acids.

Part B:

To a solution of 1.45g (3.04 mmol) of the 1:1 mixture from part A and 613 mg (4.51 mmol) of HoBT in 10 mL of DMF at 0°C was added 635 mg (3.31 mmol) of EDCl. After 30 minutes at 0°C, 5 mL of conc. aqueous ammonia was added. After 1 hour at 0°C and 14 hours at RT, ethyl acetate was added, washed with 0.2N HCl, sat'd $NaHCO_3$, brine, dried and concentrated to afford 0.64g (44%) of a 1:1 mixture of amides.

These were separated on a Whatman 10 micron partisil column using 8%-14% isopropanol/methylene chloride. The first isomer to elute was identified as

butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, [1S-[1R*(2R*, 3S*), 2S*], m/e/ = 477 (M + H).

The second isomer to elute was identified as butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]-carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-, [1S-[1R*(2S*, 3R*), 2S*], m/e = 477 (M + H).

Example 43

Preparation of pentanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl-3,3-dimethyl-, [1S-[1R*, 2S*].

Part A:

To a solution of 232 mg (0.66 mmol) of 1 and 98 mg (1.2 mmol) of pyridine in 2 mL of methylene chloride was added 95 mg (0.66 mmol) of 3,3-dimethylglutaric anhydride at RT. After 15 hours, ethyl acetate was added, washed with IN HCl, brine, dried and concentrated to afford 261 mg of crude product. Chromatography on silica gel using 5-20% methanol/methylene chloride afforded 108 mg of acid, m/e = 492 (M + H).

Part B:

To a solution of 92 mg (0.19 mmol) of product from part A and 38 mg (0.28 mmol) HoBT in 0.5 mL DMF at 0°C was added 36 mg (0.19 mmol) of EDCl. After 30 minutes at 0°C, 0.25 mL of conc. aqueous ammonia was added. After 1 hour at 0°C and 16 hours at RT, ethyl acetate was added, washed with 0.2N HCl, sat'd $NaHCO_3$, brine, dried and concentrated to afford 72 mg of crude product. This was passed through a one-inch column of basic alumina with 10% methanol/methylene chloride to afford 53 mg f desired product, m/e = 491 (M + H).

Example 44

Preparation of butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2,3-dimethyl-[1S-[1R*(2R*, 3S*), 2S*]](Isomer #1) and
Preparation of butanediamide, N-[3-[[[(1,1-dimethylethyl)amino]carbonyl](3-methylbutyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-2,3-dimethyl-[1S-[1R*(2R*, 3S*), 2S*]] (Isomer #2).

Part A:

To a solution of 1.47g (4.20 mmol) of 1 and 1.4 mL of pyridine in 9 mL of methylene chloride at RT was added 538 mg (4.20 mmol) of 2,2-dimethylsuccinic anhydride. After 15 hours, ethyl acetate was added and washed with 0.2N HCl, brine, dried and concentrated to afford 1.87g of crude product (approx. 3:1 mixture of isomer).

Part B:

To a solution of 1.85g (3.9 mmol) of crude product from part A and 887 mg (5.8 mmol) of HoBT in 10 mL of DMF at 0°C was added 809 mg (4.2 mmol) EDCl. After 30 minutes at 0°C, 6 mL of conc. aqueous ammonia was added. After 1 hour at 0°C and 15 hours at RT, ethyl acetate was added, washed with 0.2N HCl, sat'd $NaHCO_3$, brine, dried and concentrated to afford 923 mg of crude product. The two isomers were separated on a Whatman Partisil 5 column using 8-14% isopropanol/methylene chloride. The major isomer was identified as Isomer #1, m/e = 477 (M + H).

The minor isomer was identified as Isomer #2, m/e = 477 (M + H).

Example 45

This example illustrates the procedure utilized to pr pare compounds wherein the st re chemistry about the hydroxyl gr up is (S).

Part A:

A solution of 3(S)-(1,1-dimethylethoxycarbonyl)amino-1,2-(R)-epoxy-4-phenylbutane (1.00g, 3.80 mmol) and isobutylamine (5.55g, 76 mmol, 20 equiv.) in 10 mL of isopropyl alcohol was warmed to 60°C for 1 hour. The solution was cooled to room temperature and concentrated *in vacuo* and the residue recrystallized from hexane/methylene chloride to give 0.93g, 73% of [2(S), 3(S)]-N-[[[3-[(1,1-dimethylethyl)carbamoyl]amino]]-2-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine, mp 91.3 - 93.0°C.

Part B:

The product from Part A (46.3mg, 0.14 mmol) was dissolved in a mixture of 5 mL of tetrahydrofuran and 2 mL of methylene chloride and treated with tert-butylisocyanate (136.4mg, 1.376 mmol) *via* syringe. The solution was stirred at room temperature for 0.5 hour and then the solvent was removed *in vacuo*. The product, TLC on SiO_2, 1:1 hexane: Ethyl acetate had Rf = 0.74 and was used directly in the next step without further purification.

Part C:

The crude product from Part B was taken up in 10 mL of 4N hydrochloric acid in dioxane and stirred at room temperature for 0.25 hours. The solvent and excess hydrochloric acid was removed *in vacuo* whereupon the product crystallized. The solid was isolated by filtration washed with acetone and dried *in vacuo* to 3-[[(1,1-dimethylethyl)amino]carbonyl](2-methylpropyl)amino-2(S)-hydroxy-1(S)-(phenylmethyl)propylamine hydrochloride.

Part D:

A solution of N-Cbz-L-asparagine (225.5mg, 0.847 mmol) and N-hydroxybenzotriazole (182.9mg, 1.21 mm l) was dissolved in 2 mL of dimethylformamid and cooled t 0°C and then treated with EDC (170.2mg, 0.898 mmol) for 10 minutes. This mixture was th n treat d with 3-[[(1,1-dimethylethyl)amin]carb nyl](2-

methylpropyl)amino-2(S)-hydroxy-1(S)-(phenylmethyl)propylamine hydrochloride. (300.0mg, 0.807 mmol) followed by N-methylmorpholine (90.0mg, 0.888 mmol) *via* syringe. The solution was stirred at room temperature for 16 hours and then poured into 20 mL of rapidly stirring 60% saturated aqueous sodium bicarbonate solution whereupon a white precipitate formed. The solid was isolated by filtration, washed with saturated aqueous sodium bicarbonate solution, water, 5% aqueous citric acid solution, water and then dried *in vacuo* to give 319mg, 68% of butanediamide, N^1-[3-[[[(1,1-dimethylethyl)amino]carboyl](2-methylpropyl)amino]-2(S)-hydroxy-1(S)-(phenylmethyl)propyl]-2(S)-[(benzyloxycarbonyl)amino] mp 139-141°C, MH^+ m/z = 584.

EXAMPLE 46

The compounds of the present invention are effective HIV protease inhibitors. Utilizing an enzyme assay as described below, the compounds set forth in the examples herein disclosed inhibited the HIV enzyme. The preferred compounds of the present invention and their calculated IC_{50} (inhibiting concentration 50%, i.e., the concentration at which the inhibitor compound reduces enzyme activity by 50%) values are shown in Table 16. The enzyme method is described below. The substrate is 2-aminobenzoyl-Ile-Nle-Phe(p-NO_2)-Gln-ArgNH_2. The positive control is MVT-101 (Miller, M. et al, Science, 246, 1149 (1989)] The assay conditions are as follows:

Assay buffer: 20 mM sodium phosphate, pH 6.4
20% glycerol
1 mM EDTA
1 mM DTT
0.1% CHAPS

The above described substrate is dissolved in DMSO, then diluted 10 fold in assay buffer. Final substrate concentration in the assay is 80 μM.

HIV protease is diluted in the assay buffer to a final enzyme concentration of 12.3 nanomolar, based on a molecular w ight of 10,780.

The final concentration of DMSO is 14% and the final concentration of glycerol is 18%. The test compound is dissolved in DMSO and diluted in DMSO to 10x the test concentration; 10µl of the enzyme preparation is added, the materials mixed and then the mixture is incubated at ambient temperature for 15 minutes. The enzyme reaction is initiated by the addition of 40µl of substrate. The increase in fluorescence is monitored at 4 time points (0, 8, 16 and 24 minutes) at ambient temperature. Each assay is carried out in duplicate wells.

TABLE 16

Compound	IC_{50}(nanomolar)
1. 3-Thia-4,7,11-triazadodecan-12-amide, N,5-bis(1,1-dimethylethyl)-9-hydroxy-11-(3-methylbutyl)-6-oxo-8-(phenylmethyl)-1-phenyl-, 2,2-dioxide-, 5S-,(5R*,8R*,9S*)]	22nM
2. 3-Thia-4,7,11-triazadodecan-12-amide, N-(1,1-dimethylethyl)-5-(1-methylethyl)-9-hydroxy-11-(3-methylbutyl)-6-oxo-8-(phenylmethyl)-1-phenyl-, 2,2-dioxide-, [5S-,(5R*,8R*,9S*)]	29nM
3. 3-Thia-4,7,11-triazadodecan-12-amide, N-(1,1-dimethylethyl)-5-(2-amino-2-oxo-ethyl)-9-hydroxy-11-(3-methylbutyl)-6-oxo-8-(phenylmethyl)-1-phenyl-, 2,2-dioxide-, [5S-,(5R*,8R*,9S*)]	24nM

Example 47

The effectiveness of the compounds listed in Table 16 were determined in the above-described enzyme assay and in a CEM cell assay.

The HIV inhibition assay method of acutely infected cells is an automated tetrazolium based colorimetric assay essentially that reported by Pauwles et al, J. Virol. Methods 20, 309-321 (1988). Assays were performed in 96-well tissue culture plates. CEM cells, a $CD4^+$ cell line, were grown in RPMI-1640 medium (Gibco) supplemented with a 10% fetal calf serum and were then treated with polybrene (2μg/ml). An 80 μl volume of medium containing 1 x 10^4 cells was dispensed into each well of the tissue culture plate. To each well was added a 100μl volume of test compound dissolved in tissue culture medium (or medium without test compound as a control) to achieve the desired final concentration and the cells were incubated at 37°C for 1 hour. A frozen culture of HIV-1 was diluted in culture medium to a concentration of 5 x 10^4 $TCID_{50}$ per ml ($TCID_{50}$ = the dose of virus that infects 50% of cells in tissue culture), and a 20μL volume of the virus sample (containing 1000 $TCID_{50}$ of virus) was added to wells containing test compound and to wells containing only medium (infected control cells). Several wells received culture medium without virus (uninfected control cells). Likewise, the intrinsic toxicity of the test compound was determined by adding medium without virus to several wells containing test compound. In summary, the tissue culture plates contained the following experiments:

	Cells	Drug	Virus
1.	+	-	-
2.	+	+	-
3.	+	-	+
4.	+	+	+

In experiments 2 and 4 the final concentrations of test compounds were 1, 10, 100 and 500 μg/ml. Either azidothymidine (AZT) or dideoxyinosine (ddI) was included as a positive drug control. Test compounds were dissolved in DMSO and diluted into tissue culture medium so that the final DMSO concentration did not exceed 1.5% in any case. DMSO was added to all control wells at an appropriate concentration.

Following the addition of virus, cells were incubated at 37°C in a humidified, 5% CO_2 atmosphere for 7 days. Test compounds could be added on days 0, 2 and 5 if desired. On day 7, post-infection, the cells in each well were resuspended and a 100μl sample of each cell suspension was removed for assay. A 20μL volume of a 5 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to each 100μL cell suspension, and the cells were incubated for 4 hours at 27°C in a 5% CO_2 environment. During this incubation, MTT is metabolically reduced by living cells resulting in the production in the cell of a colored formazan product. To each sample was added 100μl of 10% sodium dodecylsulfate in 0.01 N HCl to lyse the cells, and samples were incubated overnight. The absorbance at 590 nm was determined for each sample using a Molecular Devices microplate reader. Absorbance values for each set of wells is compar d to assess viral control infection, uninfected c ntr l cell response as well as test comp und by cyt t xicity and antiviral efficacy.

TABLE 17

Compound	IC_{50}	EC_{50}
1. 3-Thia-4,7,11-triazadodecan-12-amide, N,5-bis(1,1-dimethylethyl)-9-hydroxy-11-(3-methylbutyl)-6-oxo-8-(phenylmethyl)-1-phenyl-, 2,2-dioxide-, [5S-,(5R*,8R*,9S*)]	22nM	510nM
2. 3-Thia-4,7,11-triazadodecan-12-amide, N-(1,1-dimethylethyl)-5-(1-methylethyl)-9-hydroxy-11-(3-methylbutyl)-6-oxo-8-(phenylmethyl)-1-phenyl-, 2,2-dioxide-, [5S-,(5R*,8R*,9S*)]	29nM	440nM

The compounds of the present invention are effective antiviral compounds and, in particular, are effective retroviral inhibitors as shown above. Thus, the subject compounds are effective HIV protease inhibitors. It is contemplated that the subject compounds will also inhibit other viruses such as HIV, human T-cell leukemia virus, respiratory syncytial virus, hepadnavirus, cytomegalovirus and picornavirus.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydr bromid , hydr iodid , 2-hydroxy-ethan sulfonate, lactate, mal ate, methanesulf nate, nicotinate, 2-naphthalenesulfonate, xalat , palm at , pectinate, p rsulfat , 3-phenylpropionate, picrate, pivalate,

pr pionate, succinate, tartrate, thiocyanat , tosylate, mesylate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001 to 10 mg/kg body weight daily and more usually 0.01 to 1 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route f administration, rate of excretion, drug combination, and the s verity of the particular disease underg ing therapy.

The compounds of the present invention may be administ red orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powd rs, and granules. In such solid dosage f rms, the activ compound may be admixed with at least ne inert dilu nt such as sucr se lactose or starch. Such dosage f rms may als comprise,

as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more immunomodulators, antiviral agents or other antiinfective agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

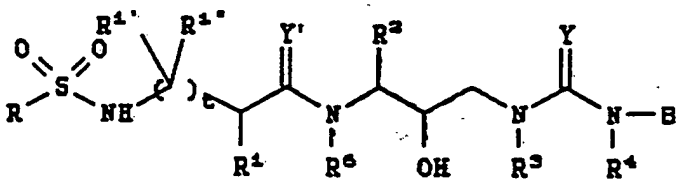
The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make vari us

changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A compound represented by the formula:



wherein

R represents alkyl, alkenyl, hydroxyalkyl, cycloalky, cycloalkyalky, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals;

t represents 0 or 1;

R^1 represents $-CH_2SO_2NH_2$, alkyl and cycloalkyl radicals and amino acid side chains selected from asparagine, S-methyl cysteine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, allo-isoleucine, leucine, tert-leucine, phenylalanine, ornithine, alanine, threonine, allo-threonine, isoleucine, histidine, norleucine, valine, glutamine, serine, aspartic acid, beta-cyano alanine side chains;

$R^{1'}$ and $R^{1''}$ independently represent hydrogen and radicals as defined for R^1;

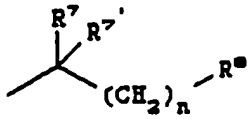
R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals optionally substituted with a group selected from $-OR^9$, $-SR^9$, and halogen radicals, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, alkenyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals;

Y and Y' independently represent O and S;

R^4 and R^5 independently represent radicals as d fined for R^3, or R^4 and R^5 together with the nitr gen atom to which they are bonded represent heterocycloalkyl and heteroaryl radicals; R^6 represents hydrogen and radicals as defined for R^3;

B represents R^5 and radicals represented by the formula:

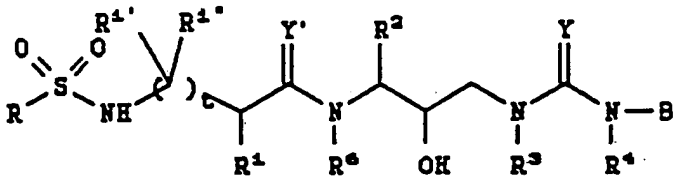


wherein

n represents an integer of from 0 to 6, R^7 and $R^{7'}$ independently represent radicals as defined for R^3 and amino acid side chains selected from the group consisting of valine, isoleucine, glycine, alanine, allo-isoleucine, asparagine, leucine, glutamine, and t-butylglycine or R^7 and $R^{7'}$ together with the carbon atom to which they are attached form a cycloalkyl radical; and R^8 represents cyano, hydroxyl, alkyl, alkoxy, cycloalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl radicals and radicals represented by the formulas $C(O)R^{16}$, CO_2R^{16}, SO_2R^{16}, SR^{16}, $CONR^{16}R^{17}$, OR^{16}, CF_3 and $NR^{16}R^{17}$ wherein R^{16} and R^{17} independently represent hydrogen and radicals as defined for R^3 or R^{16} and R^{17} together with a nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radicals.

R^6 represents hydrogen and radicals as defined for R^3;

2. Compound represented by the formula:



wherein

R represents alkyl, alkenyl, hydroxyalkyl, cycloalky, cycloalkyalky, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals;

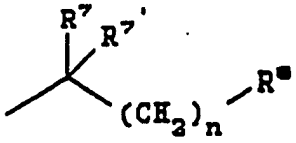
R^1 represents $-CH_2SO_2NH_2$, alkyl and cycloalkyl radicals, and amino acid side chains selected from the group of asparagine, S-methyl cysteine and the sulfoxide (SO) and sulfone (SO_2) derivatives thereof, histidine, norleucine, glutamine, glycine, allo-isoleucine, alanine, threonine, isoleucine, leucine, tert-leucine, phenylalanine, ornithine, allo-threonine, serine, aspartic acid, beta-cyano alanine and valine side chains;

$R^{1'}$ and $R^{1''}$ independently represent hydrogen and radicals as defined for R^1;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl, and aralkyl radicals, which radicals are optionally substituted with a group selected from halogen radicals and $-OR^9$ and SR^9 wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, alkenyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals;

R^4 represents hydrogen and radicals as defined by R^3; B represents radicals represented by the formula:



wherein
n represents an integer of from 0 to 6, R^7 and $R^{7'}$ independently represent radicals as defined for R^3 and amino acid side chains selected from the group consisting of valine, isoleucine, glycine, alanine, allo-isoleucine, asparagine, leucine, glutamine, and t-butylglycine or R^7 and $R^{7'}$ together with the carbon atom to which they are attached form a cycloalkyl radical; and R^8 represents cyano, hydroxyl, alkyl, cycloalkyl, aryl, aralkyl, heterocycloalkyl and heteroaryl radicals and radicals represented by the formulas $C(O)R^{16}$, CO_2R^{16}, SO_2R^{16}, SR^{16}, $CONR^{16}R^{17}$, OR^{16}, CF_3 and $NR^{16}R^{17}$ wherein R^{16} and R^{17} independently represent hydrogen and radicals as defined for R^3 or R^{16} and R^{17} together with a nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radicals;
R^6 represents hydrogen and radicals as defined for R^3;
t represents 0 or 1; and
Y represents O and S.

3. Compound of Claim 2 wherein R represents aryl and aralkyl radicals.

4. Compound of Claim 2 wherein R represents alkyl and aralkyl radicals.

5. Compound of Claim 2 wherein R represents methyl, ethyl and N-butyl radicals.

6. Compound of Claim 2 wherein R represents benzyl, phenethyl, and naphthyl radicals.

7. Compound f Claim 2 wherein R^1 represents alkyl radicals and amino acid side chains selected from th group consisting f asparagine, valin , threonin , allo-threonine, isoleucin , S-methyl cyst ine and the

sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine.

8. C mpound of Claim 2 wherein R^1 represents methyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine, threonine and allo-threonine side chains.

9. Compound of Claim 2 wherein R^1 represents methyl and t-butyl radicals.

10. Compound of Claim 2 wherein R^1 represents a t-butyl radical.

11. Compound of Claim 2 wherein R^1 represents amino acid side chains selected from asparagine, valine, alanine and isoleucine side chains.

12. Compound of Claim 2 wherein R^1 represents amino acid side chains selected from asparagine, iso-leucine and valine side chains.

13. Compound of Claim 2 wherein R^1 represents an asparagine side chain.

14. Compound of Claim 2 wherein R^1 represents a t-butyl radical and an asparagine side chain.

15. Compound of Claim 2 wherein R^1 represents a methyl radical when t is 1.

16. Compound of Claim 2 wherein t is 0.

17. Compound of Claim 2 wherein t is 1.

18. Compound of Claim 2 wherein R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula $-OR^9$ and $-SR^9$ wherein R^9 represents alkyl radicals.

19. Compound of Claim 2 wherein R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals.

20. Compound of Claim 2 wherein R^2 represents aralkyl radicals.

21. Comp und f Claim 2 wh rein R^2 repres nts $CH_3SCH_2CH_2-$, iso-butyl, n-butyl, benzyl, 2-naphthylmethyl and cyclohexylmethyl radicals.

22. Compound f Claim 2 wherein R^2 repr sents an n-butyl and is -butyl radicals.

23. Compound of Claim 2 wherein R^2 represents benzyl and 2-naphthylmethyl radicals.

24. Compound of Claim 2 wherein R^2 represents a cyclohexylmethyl radical.

25. Compound of Claim 2 wherein R^3, represents alkyl, alkenyl, hydroxyalkyl, cycloalkyl, cycloalkyl-alkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals.

26. Compound of Claim 25 wherein R_4 represents hydrogen.

27. Compound of Claim 25 wherein R^3 and R^4 independently represent alkyl and alkenyl radicals.

28. Compound of Claim 26 wherein R^3 and R^4 independently represent alkyl and hydroxyalkyl radicals.

29. Compound of Claim 26 wherein R^3 and R^4 independently represent alkyl, cycloalkyl and cycloalkylalkyl radicals.

30. Compound of Claim 26 wherein R^7 and $R^{7'}$ independently represent alkyl and aralkyl radicals or together with the carbon atom to which they are attached form a cycloalkyl radical having from 3 to about 6 carbon atoms.

31. Compound of Claim 26 wherein R^7 and $R^{7'}$ independently represent methyl and ethyl radicals or R^7 and $R^{7'}$ together with the carbon atom to which they are attached represent cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl radicals.

32. Compound of Claim 26 wherein R^7 and $R^{7'}$ are both methyl.

33. Compound of Claim 2 wherein R^3 represents alkyl radicals having from about 2 to about 5 carbon atoms.

34. Compound of Claim 2 wherein R^3 represents i-butyl, neo-p ntyl, i-amyl and n-butyl radicals.

35. Comp und f Claim 2 wherein R^7 and $R^{7'}$ together with the carbon atom t which th y are attached

r pr sent cyclopropyl, cyclobutyl, cyclopentyl and cycloh xyl radicals.

36. Compound of Claim 2 wherein R^3 represents benzyl, para-fluorobenzyl, para-methoxybenzyl, para-methylbenzyl, and 2-naphthylmethyl radicals and R^4 represents t-butyl.

37. Compound of Claim 32 where n is O and R^8 represents alkylcarbonyl, aryl, aroyl, aralkanoyl, cyano and alkoxycarbonyl.

38. Compound of Claim 37 where R^8 represents methylcarbonyl, phenyl and cyano.

39. Compound of Claim 37 where R^8 represents methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, t-butoxycarbonyl and benzyloxycarbonyl.

40. Compound of Claim 37 where R^8 represents -COOH.

41. Compound of Claim 32 where n is 1 or 2 and R^8 represents alkoxycarbonyl, hydroxycarbonyl, arylsulfonyl, alkylsulfonyl, alkylthio, hydroxyl, alkoxy, aryloxy, aryl, heteroaryl and N,N-dialkylcarbamoyl.

42. Compound of Claim 32 where n is 1 or 2 and R^8 represents N,N-dialkylamino or N-heterocyclylamine.

43. Compound of Claim 41 where n is 1 and R^8 represents methoxycarbonyl and hydroxycarbonyl.

44. Compound of Claim 41 where n is 1 and R^8 represents methylsulfonyl, methythio and phonylsulfonyl.

45. Compound of Claim 41 where n is 1 and R^8 is hydroxy or methoxy.

46. Compound of Claim 41 where n is 1 and R^8 is phenyl or 4-pyridyl or 4-pyridyl N-oxide.

47. Compound of Claim 41 where n is 1 and R^8 is N,N-dimethylcarbamoyl.

48. Compound f Claim 42 where R^8 represents N,N-dimethylamino, 1-piperidinyl, 4-m rph linyl, 4-(N-m thyl)piperazinyl, 1-pyrrolidinyl.

49. Compound of Claim 48 where n is 1 and R^8 represents 4-morph linyl.

50. Compound of Claim 48 where n is 2 and R^8 represents 4-morpholinyl, N,N-dimethylamino and 4-(N-methyl)piperazinyl.

51. Compound of Claim 35 where n is O and R^8 represents methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, t-butoxycarbonyl and methylcarbonyl.

52. Compound of Claim 35 where n is O and R^8 represents methylcarbonyl.

53. Compound of Claim 2 wherein R^3 represents heteroaralkyl radicals.

54. Compound of Claim 2 wherein R^3 is a p-fluorobenzyl radical.

55. Compound of Claim 2 wherein R^3 is a 4-pyridylmethyl radical.

56. Compound of Claim 2 wherein R^3 represents an i-amyl radical.

57. Compound of Claim 2 wherein R^3 represents an isobutyl radical.

58. Compound of Claim 2 wherein R^1 and $R^{1'}$ are both hydrogen and $R^{1''}$ represents an alkyl radical having from 1 to about 4 carbon atoms.

59. Compound of Claim 2 wherein R^1 and $R^{1'}$ are both hydrogen and $R^{1''}$ represents $-CH_2SO_2NH_2$, alkyl and cycloalkyl radicals and amino acid side chains selected from asparagine, S-methyl cystine and the sulfone and sulfoxide derivatives thereof, histidine, norleucine, glutamine, glycine, allo-isoleucine, alanine, threonine, isoleucine, leucine, tert-leucine, phenylalanine, ornithine, allo-threonine and valine side chains.

60. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

61. A pharmaceutical composition comprising a compound of Claim 2 and a pharmaceutically acceptable carrier.

62. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 60.

63. Method of Claim 62 wherein the retroviral protease is HIV protease.

64. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 60.

65. Method of Claim 64 wherein the retroviral infection is an HIV infection.

66. Method for treating AIDS comprising administering an effective amount of a composition of Claim 60.

67. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 61.

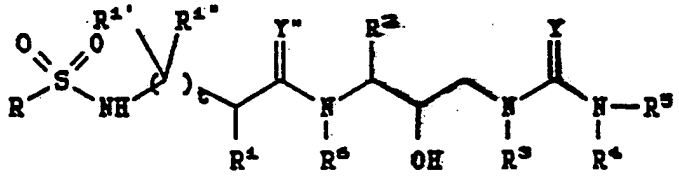
68. Method of Claim 67 wherein the retroviral protease is HIV protease.

69. Method for treating a retroviral infection comprising administering an effective amount of a composition of Claim 61.

70. Method of Claim 69 wherein the retroviral infection is an HIV infection.

71. Method for treating AIDS comprising administering an effective amount of a composition of Claim 61.

72. Compound represented by the formula:



wherein

R represents radicals as defined for R^3;

R^1 represents $-CH_2SO_2NH_2$, alkyl and cycloalkyl radicals and amino acid side chains selected from asparagine,

S-methyl cyst ine and the corresponding sulfoxide and sulfone derivatives thereof, glycine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, threonine, allo-threonine, isoleucine, histidine, norleucine, valine, glutamine, serine, aspartic acid and beta-cyano alanine side chains;

$R^{1'}$ and $R^{1''}$ independently represent hydrogen and radicals as defined for R^1;

R^2 represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals optionally substituted with a group selected from $-OR^9$, $-SR^9$, and halogen radicals, wherein R^9 represents hydrogen and alkyl radicals;

R^3 represents alkyl, alkenyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, heteroaryl, aralkyl, and heteroaralkyl radicals;

R^4 and R^5 independently represent hydrogen and radicals as defined for R^3, or R^4 and R^5 together with the nitrogen atom to which they are bonded represent heterocycloalkyl and heteroaryl radicals; and

Y and Y' independently represent O and S.

73. Compound of Claim 72 wherein t is O.

74. Compound of Claim 72 wherein R^1 represents hydrogen and alkyl radicals.

75. Compound of Claim 72 wherein R^1 represents alkyl radicals having from 1 to about 4 carbon atoms.

76. Compound of Claim 72 herein R^1 represents methyl, ethyl, isopropyl and t-butyl radicals.

77. Compound of Claim 72 wherein $R^{1'}$ and $R^{1''}$ independently represent hydrogen and alkyl radials.

78. Compound of Claim 72 wherein $R^{1'}$ and $R^{1''}$ independently represent hydrogen and methyl radicals.

79. Compound of Claim 72 wherein $R^{1'}$ is hydrogen and $R^{1''}$ is an alkyl radical.

80. Compound of Claim 72 wherein R repres nts alkyl, aryl and aralkyl radicals.

81. Compound of Claim 72 wherein R is selected from methyl, benzyl and phenethyl radicals.

82. Compound of Claim 72 wherein R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula $-OR^9$ and $-SR^9$ wherein R^9 represents alkyl radicals.

83. Compound of Claim 72 wherein R^2 represents alkyl, cycloalkylalkyl and aralkyl radicals.

84. Compound of Claim 72 wherein R^2 represents aralkyl radicals.

85. Compound of Claim 72 wherein R^2 represents $CH_3SCH_2CH_2-$, iso-butyl, n-butyl, benzyl, 2-naphthylmethyl and cyclohexylmethyl radicals.

86. Compound of Claim 72 wherein R^2 represents an n-butyl and iso-butyl radicals.

87. Compound of Claim 72 wherein R^2 represents benzyl and 2-naphthylmethyl radicals.

88. Compound of Claim 72 wherein R^2 represents a cyclohexylmethyl radical.

89. Compound of Claim 72 wherein R^3, represents alkyl, alkenyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals.

90. Compound of Claim 89 wherein R^4 represents hydrogen.

91. Compound of Claim 89 wherein R^3 represents alkyl and alkenyl radicals.

92. Compound of Claim 90 wherein R^3 represents alkyl and hydroxyalkyl radicals.

93. Compound of Claim 90 wherein R^3 represents alkyl, cycloalkyl and cycloalkylalkyl radicals.

94. Compound of Claim 90 wherein R^3 represents alkyl, heter cycloalkyl and heterocycloalkylalkyl radicals.

95. Compound of Claim 90 wherein R^3 represents alkyl, aryl and aralkyl radicals.

96. Compound of Claim 90 wherein R^3, R^4 and R^5 independently represent alkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, and heteroaralkyl radicals.

97. Compound of Claim 72 wherein R^3 represents alkyl radicals having from about 2 to about 5 carbon atoms.

98. Compound of Claim 72 wherein R^3 represents i-butyl, neo-pentyl, i-amyl, and n-butyl radicals.

99. Compound of Claim 72 wherein R^5 represents hydrogen.

100. Compound of Claim 72 wherein R^3 represents benzyl, para-fluorobenzyl, para-methoxybenzyl, para-methylbenzyl, and 2-naphthylmethyl radicals.

101. Compound of Claim 72 wherein R^5 represents hydrogen, alkyl and cycloalkyl radicals.

102. Compound of Claim 72 wherein R^4 and R^5 independently represent ethyl and t-butyl radicals or R^4 and R^5 together with the nitrogen atom to which they are attached represent pyrrolidinylpiperidinyl, morpholinyl and piperazinyl radicals.

103. Compound of Claim 72 wherein R^4 and R^5 are both ethyl radicals.

104. Compound of Claim 72 wherein R^3 represents alkyl radicals having from about 2 to about 5 carbon atoms.

105. Compound of Claim 72 wherein R^4 and R^5 independently represent alkyl and cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl radicals.

106. A pharmaceutical composition comprising a compound of Claim 72 and a pharmaceutically acceptable carrier.

107. Method of inhibiting a retroviral proteas comprising administering a protease inhibiting am unt f a composition f Claim 106.

108. Method of Claim 107 wherein the retroviral protease is HIV protease.

109. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 106.

110. Method of Claim 109 wherein the retroviral infection is an HIV infection.

111. Method for treating AIDS comprising administering an effective amount of a composition of Claim 106.

INTERNATIONAL SEARCH REPOT

International Application No PCT/US 91/08593

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 215/48 C 07 D 295/13 C 07 C 311/46
C 07 C 311/47 C 07 C 317/50 C 07 C 323/60 C 07 C 275/14

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D C 07 C C 07 K A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	US,A,4599198 (D.J. HOOVER) 08 July 1986 (cited in the application)	
A	EP,A,0264795 (MERCK) 27 April 1988 (cited in the application)	

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03-02-1992	08. 04. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Natalie Weinberg

FURTHER INFORMATI N CONTINUED FR M THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 1-111 because they relate to subject matter not required to be searched by this Authority, namely:

The use of terms such as heteroaryl and heterocyclyl are in contradiction to the requirements of Art. 6 PCT. The search was performed on the basis of those claims which are clear and concise and of those examples in the description which are complete and correct.

2. [X] Claim numbers ** because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

** Remark: Although claims 62-71,107-111 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9108593 SA 55041

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 24/03/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4599198	08-07-86	US-A- 4668769	26-05-87
		AU-B- 598913	05-07-90
		AU-A- 1239288	02-06-88
		AU-B- 569821	18-02-88
		AU-A- 6079086	14-05-87
		AU-A- 6385090	10-01-91
		EP-A- 0211580	25-02-87
		JP-A- 62033141	13-02-87
EP-A- 0264795	27-04-88	DE-A- 3635907	28-04-88
		AU-A- 7982387	28-04-88
		JP-A- 63112548	17-05-88
		ZA-A- 8707950	26-04-88